(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055531 A1

(51) International Patent Classification[7]: C07J 43/00, A61K 31/58, A61P 5/44

(21) International Application Number: PCT/HR02/00001

(22) International Filing Date: 3 January 2002 (03.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20010018A 9 January 2001 (09.01.2001) HR

(71) Applicant (*for all designated States except US*): **PLIVA D.D.** [HR/HR]; Ulica Grada Vikovara 49, 10 000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **MERCEP, Mladen** [HR/HR]; Majstora Radonje 10, H-10 000 Zagreb (HR). **MESIC, Milan** [HR/HR]; Slavenskog 8, H-10 000 Zagreb (HR). **TOMASKOVIC, Linda** [HR/HR]; Lascinska 119, H-10 000 Zagreb (HR). **KOMAC, Marijana** [HR/HR]; Dragozeticka 11, H-10 000 Zagreb (HR). **HRVACIC, Boska** [HR/HR]; Skolska 45, H-10410 Velika Gorica (HR). **MARKOVIC, Stribor** [HR/HR]; Sarajevska 2A, H-47 000 Karlovac (HR).

(74) Common Representative: **PLIVA D.D.**; Ulica Grada Vikovara 49, H-10 000 Zagreb (HR).

(81) Designated States (*national*): BA, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IN, IS, JP, KP, LT, LV, MK, PL, SI, SK, UA, US, UZ, YU.

(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:

— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/055531 A1

(54) Title: CONJUGATES OF IMMUNE CELL SPECIFIC MACROLIDE COMPOUNDS WITH ANTI-INFLAMMATORY COMPOUNDS FOR IMPROVED CELLULAR TARGETING OF ANTI-INFLAMMATORY THERAPY

(57) Abstract: The present invention relates to novel compounds represented by the structure I and pharmaceutical preparations thereof for the treatment of inflammatory diseases in humans and animals.

CONJUGATES OF IMMUNE CELL SPECIFIC MACROLIDE COMPOUNDS WITH ANTI-INFLAMMATORY COMPOUNDS FOR IMPROVED CELLULAR TARGETING OF ANTI-INFLAMMATORY THERAPY

Technical problem

The present invention relates to new anti-inflammatory compounds represented by the general structure I, to their salts and solvates, to processes for their preparation and to the use of these compounds in the treatment of inflammatory diseases and conditions in humans and animals.

Prior art

Anti-inflammatory medicaments could be classified into those of steroid and of nonsteroid type. Steroid anti-inflammatory compounds are still the most effective ones in the treatment of inflammatory diseases and conditions such as asthma, chronic obstructive pulmonary disease, inflammatory nasal diseases such as allergic rhinitis, nasal polyps, intestinal diseases such as Crohn's disease, colitis, ulcerative colitis, dermatological inflammations such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis, conjunctivitis and rheumatoid arthritis. In addition to the excellent potency and effectiveness, medicaments of this type also possess numerous unfavourable effects e.g. on carbohydrate metabolism, calcium resorption, secretion of endogenous corticosteroids as well as on physiological functions of hypophysis, adrenal cortex and thymus. Hitherto developed steroids are highly effective against inflammation conditions and processes since they inhibit many inflammation mediators whereas their systemic unfavourable effects are diminished. Patent applications WO 94/13690, WO 94/14834, WO 92/13873 and WO 92/13872 disclose so-called "soft" steroids or hydrolysable corticosteroids designed for topical application on the inflammation site, whereas their systemic unfavourable effect is diminished due to the instability of "soft" steroids in serum, wherein the active steroid very rapidly hydrolizes into the inactive form. An ideal steroid, however, without unfavourable effects in a long-term and continuous treatment as required for the control of diseases such as asthma or Crohn's disease has yet to be found and it has

been worked intensively on finding and developing steroids with an improved therapeutic profile.

Nonsteroid anti-inflammatory medicaments of different mechanisms act on particular inflammation mediators, thus providing a therapeutical effect. Due to different action mechanisms and differences in the inhibition of particular inflammation mediators, the steroid and nonsteroid medicaments possess different profiles of anti-inflammation effects, hence in particular conditions they are used alternatively or preferentially. Unfortunately, nonsteroid anti-inflammatory medicaments are not absolutely specific either and demonstrate unfavourable effects when used in greater concentrations or over long periods. It is known that many nonsteroid anti-inflammatory medicaments act as inhibitors of endogenous COX-1 enzyme, which is very important in maintaining the integrity of the gastric mucosa. Thus, the use of these medicaments causes injuries of the gastric mucosa and bleeding in numerous patients. For some anti-inflammatory compounds (theophylline) it is known that their therapeutic index is very narrow, which limits their usage.

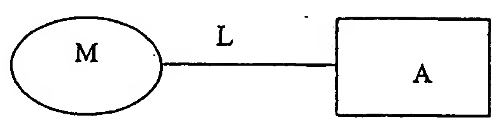
Macrolide antibiotics accumulate within different cells of organism, especially within phagocyte cells such as mononuclear peripheral blood cells, peritoneal and alveolar macrophages as well as in the liquid surrounding the bronchoalveolar epithelium (Glaude R. P. et al, *Antimicrob. Agents Chemother., 33* **1989**, 277-282; Olsen K. M. et al, *Antimicrob. Agents Chemother., 40* **1996**, 2582-2585). Moreover, in the literature also relatively weak inflammatory effects of some macrolides are described. Thus, there has recently been described the anti-inflammatory effect of erythromycin derivatives (*J. Antimicrob. Chemother., 41,* **1998**, 37-46; WO 00/42055) and azithromycin derivatives (EP 0283055). An anti-inflammatory effect of some macrolides is also known from *in vitro* and *in vivo* studies in experimental animals such as at zimosane-induced peritonitis in mice (*J. Antimicrob. Chemother. 30,* **1992,** 339-348) and at endotoxine-induced neutrophil accumulation in rat trachea (*J. Immunol. 159,* **1997**, 3395-4005). The modulating effect of macrolides upon cytokines

such as interleukin 8 (IL-8) (*Am. J. Respir. Crit. Care. Med. 156,* 1997, 266-271) or interleukin 5 (IL-5) (EP 0775489 and EP 0771564) is known as well.

Technical Solution

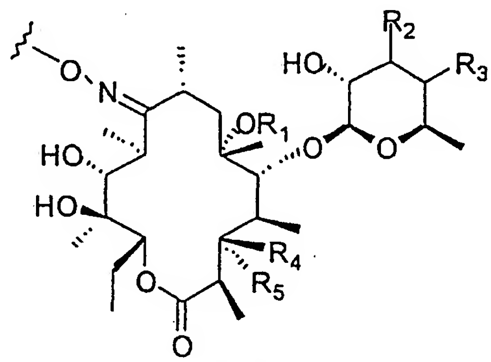
Compounds of the structure I differ from hitherto known ones in their new action mechanism characterized by selective accumulation in the organs and cells targeted in the above-mentioned inflammation conditions and diseases. Such action of the new compounds represented by the structure I arises from the macrolide portion **M** due to the said specific pharmacokinetic properties. Such pharmacokinetic properties enable the compounds represented by the structure I to act exclusively in the inflammation site just in the inflammation cells themselves by inhibiting the production of inflammation mediators. In such a manner the unfavourable systemic effect of both corticosteroids and nonsteroid anti-inflammatory compounds is avoided. After topical application the molecules rapidly accumulate in inflammation cells, wherein they act by inhibiting the production of cytokines and chemokines as well as other inflammation mediators and thus suppressing the inflammation. According to the known and established prior art, the compounds represented by the structure I, which are the object of the present invention, their pharmacologically acceptable salts and pharmaceutical preparations comprising them have hitherto not been described. Moreover, none of the compounds being the object of the present invention has been described either as an anti-inflammatory substance or as an inhibitor of eosinophilic accumulation in inflammation tissues.

The object of the present invention are new compounds, their salts and solvates represented by the structure I



wherein **M** represents a macrolide subunit possessing the property of accumulation in inflammatory cells, **A** represents an anti-inflammatory subunit that can be steroid or nonsteroid and **L** represents a chain linking **M** and **A**,
as well as an improved therapeutic effect of these compounds in treating inflammation diseases and conditions.

More specifically, this invention relates to compounds, their salts and solvates represented by the structure I, wherein **M** represents a macrolide subunit represented by the formulas



M1

wherein

R_1 is hydrogen or a methyl group,

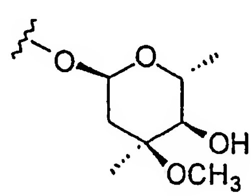
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

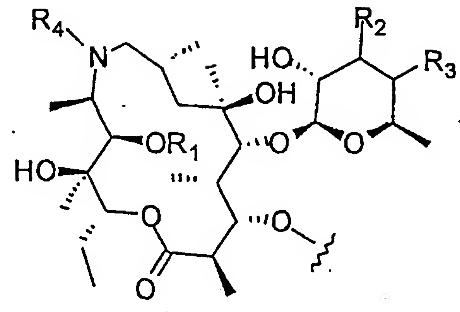
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_4 and R_5 may also together form a carbonyl group, with the proviso that R_1 is then a methyl group;



M2

wherein

R_1 is hydrogen or a methyl group,

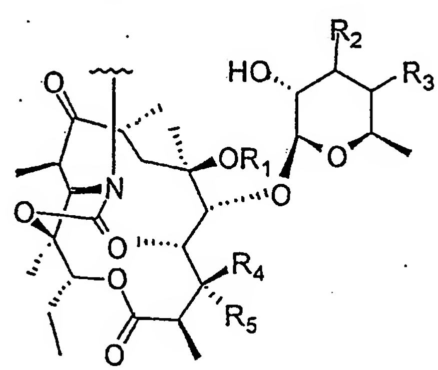
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group;



M3

wherein

R_1 is hydrogen or a methyl group,

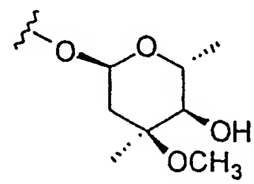
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

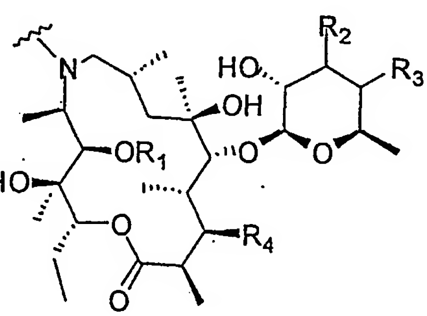
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_4 and R_5 may also together form a carbonyl group, with the proviso that R_1 is then a methyl group;



M4

wherein

R_1 is hydrogen or a methyl group,

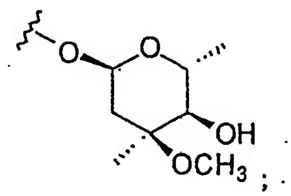
R_2 and R_3 are both hydrogen or together form a bond, or

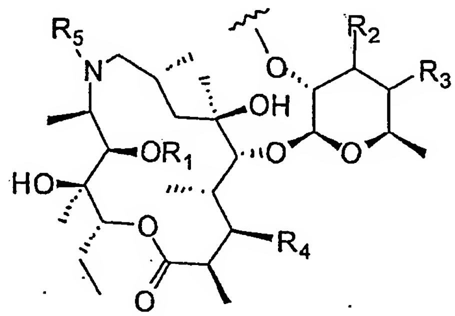
R_2 is an amino group represented by the substructure

-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure





M5

wherein

R_1 is hydrogen or a methyl group,

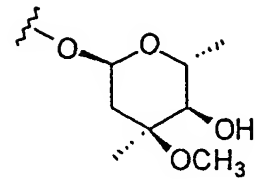
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

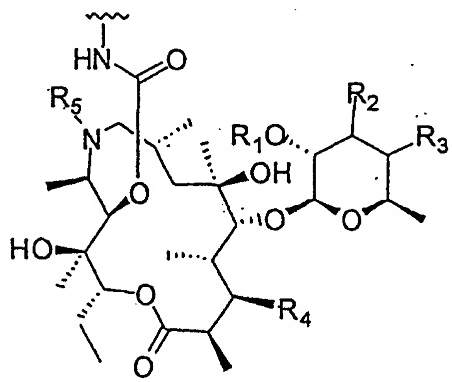
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a a hydroxyl or cladinosyl group represented by the structure



R_5 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group;



M6

wherein

R_1 is hydrogen or an acetyl group,

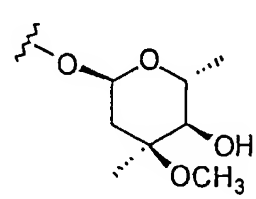
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is amino group represented by the substructure

-NR'R''

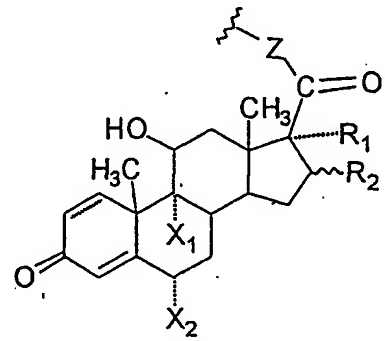
wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_5 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group,

and A is an anti-inflammatory subunit represented by the formulas:



A1

wherein Z represents oxygen or a NH group, R_1 is hydrogen or a hydroxyl or O-acyl or O-alkyl group,

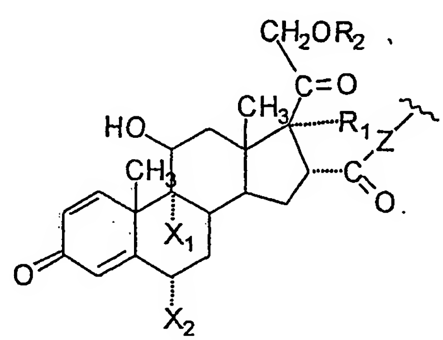
R_2 represents hydrogen or a methyl group, which may be oriented in α- or β-position,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine,

1,2-position may represent a double or a single carbon-carbon bond;



A2

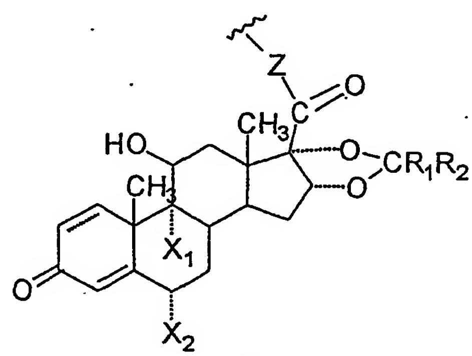
wherein Z represents oxygen or a NH group, R_1 is hydrogen or a hydroxyl or O-acyl or O-alkyl group,

R_2 represents hydrogen or an acyl group,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A3

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond, wherein Z represents oxygen or a NH group,

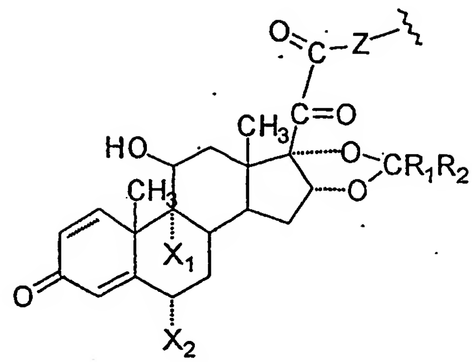
R_1 is hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms, with the proviso that R_1 and R_2 are not simultaneously hydrogen,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A4

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond, wherein Z is oxygen or a NH group,

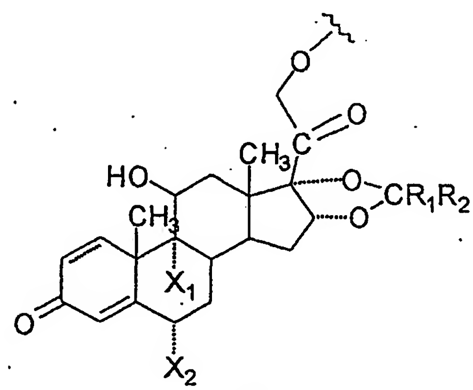
R_1 is hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms with the proviso that R_1 and R_2 are not simultaneously hydrogen,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A5

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond,

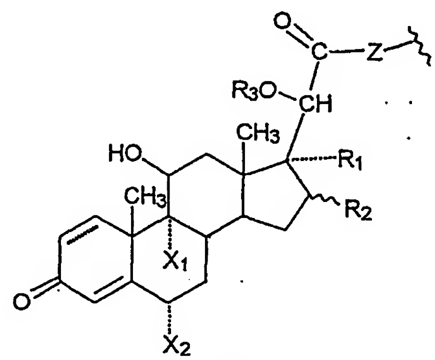
R_1 is hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms with the proviso that R_1 and R_2 are not simultaneously hydrogen,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine, preferably fluorine;



A6

wherein Z is oxygen or a NH group, R_1 is hydrogen or a hydroxyl group with a free hydrogen or a hydroxyl group or O-acyl or O-alkyl group,

R_2 is hydrogen or a methyl group, which may be oriented in α- or β-position,

R_3 is hydrogen or a radical of an acid having 1-4 carbon atoms,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine, preferably fluorine,

1,2-position may represent a double or single carbon-carbon bond,

and **L** is a chain with the formula $-CR_1R_2(CR_3R_4)_nCR_5R_6-$,

wherein R_1, R_2, R_3, R_4, R_5, R_6 may be hydrogen, C_1-C_4-alkyl, aryl, metoxy, halogen, hydroxy or mercapto groups, wherein n is 1-10, and

one or more $-CR_3R_4-$ groups may be substituted with oxygen, sulphur, an aromatic nucleus or an amino group additionally bearing hydrogen or a C_1-C_4 alkyl or aryl group,

or R_1, R_2, R_3, R_4, R_5, R_6 may also together form one or more double or triple bonds in a chain, thus forming alkenyl or alkinyl, with the proviso that at least one methylene group is situated at the end of linking **L** group.

The chain covalently links subunits **M** and **A** *via* functional groups such as amides, ureates, carbamates, ethers, esters or *via* alkyl-alkyl or carbon-carbon bonds.

The terms used in the present invention are defined as stated hereinafter if not specified otherwise.

"Alkyl" means a monovalent alkane (hydrocarbon), wherefrom a radical is derived, which may be a straight-chain one, a branched-chain one, a cyclic one or a combination of straight-chain and cyclic hydrocarbons and branched-chain and cyclic hydrocarbons. Preferred straight-chain or branched-chain alkyls include methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl and *t*-butyl groups. Preferable cycloalkyls include cyclopentyl and cyclohexyl groups. Alkyl also represents both a straight-chain or a branched-chain alkyl group including or being interrupted by a cycloalkyl portion.

"Alkenyl" means a hydrocarbon radical, which is a straight-chain one, a branched-chain one, a cyclic one or a combination of straight-chain and cyclic hydrocarbons and branched-chain and cyclic hydrocarbons and comprises at least one double carbon-carbon bond. Mainly ethenyl, propenyl, butenyl and cyclohexenyl groups are meant thereby. As already mentioned above for "alkyls", also alkenyls may be straight-chain, branched-chain or cyclic ones, where a part of the alkenyl group may include double bonds and may also be substituted when a substituted alkenyl group is in question. Alkenyl also represents both a straight-chain or a branched-chain alkenyl group including or being interrupted by a cycloalkenyl portion.

"Alkynyl" means a hydrocarbon radical, which is a straight-chain or a branched-chain one and includes at least one and at most three triple carbon-carbon bonds. Mainly ethynyl, propynyl and butynyl groups are meant thereby.

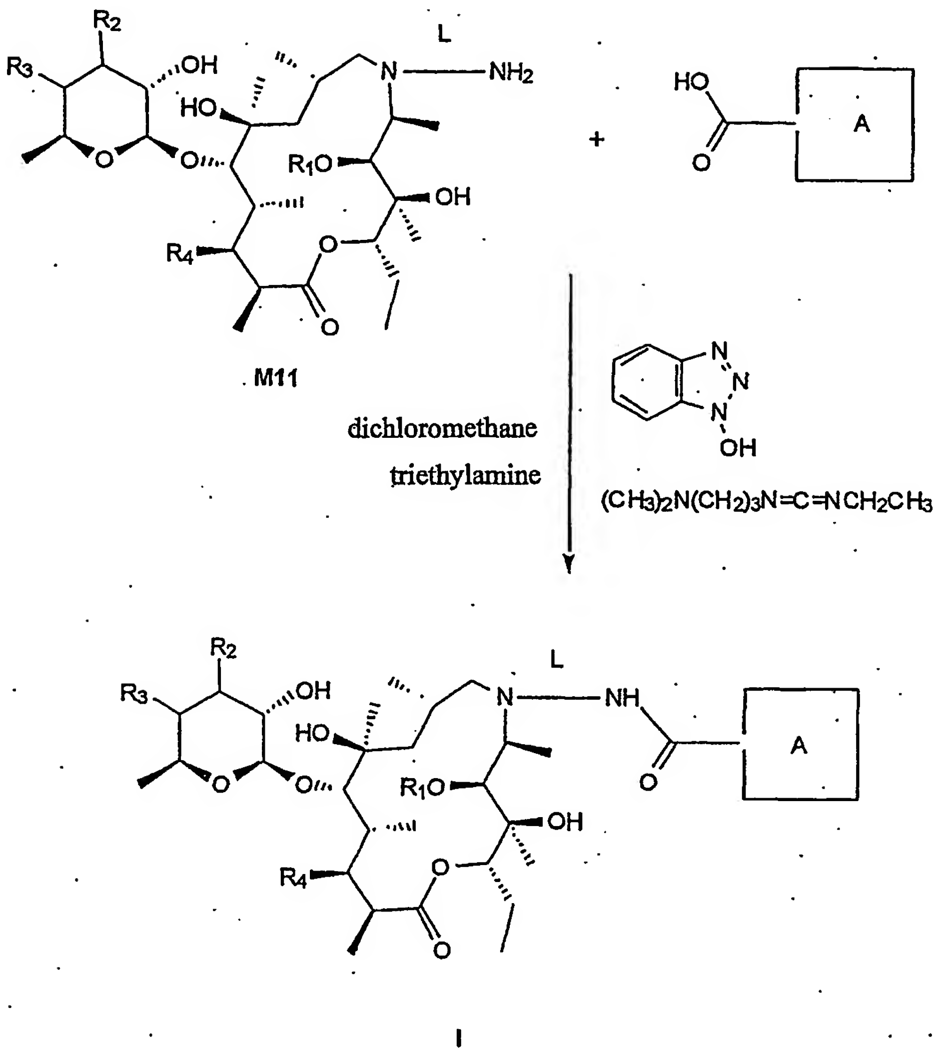
"Aryl" means an aromatic ring such as phenyl group, substituted phenyl or similar groups as well as rings that are fused such as naphtyl and the like. Aryl includes at least one ring having at least 6 carbon atoms or two rings having together 10 carbon

atoms, possessing alternating double (resonance) bonds between carbon atoms (mainly phenyl and naphtyl rings). Aryl groups may be additionally substituted with one or two substituents, which may be halogen (fluorine, chlorine or bromine) and hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or aryloxy, C_1-C_7 alkylthio or arylthio, alkylsulfonyl, ciano or amino groups.

A further object of the present invention relates to a process for the preparation of compounds represented by the structure I.

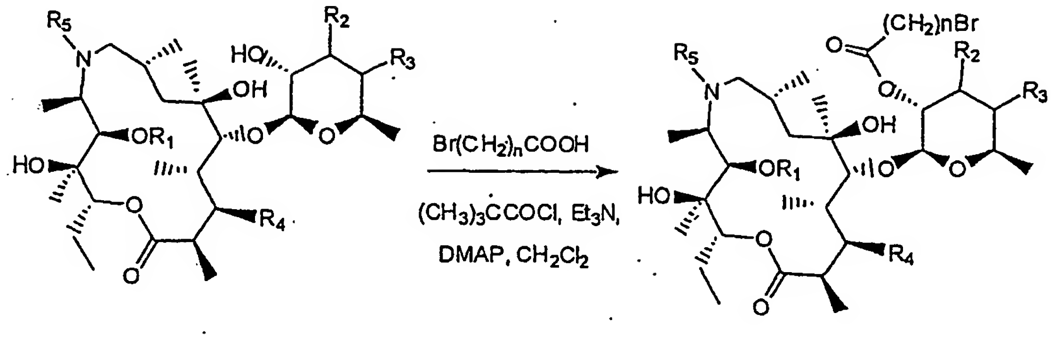
These compounds can be prepared from the corresponding steroid part represented by the general structures **A1** to **A6**, wherein all radicals and symbols have the meanings as defined for substructures **A1** to **A6**, and macrolide intermediates represented by the general structures **M1** to **M6** by linking them *via* appropriate functional **L** groups. In an analogous manner, it is also possible to prepare compounds represented by the structure I with nonsteroid anti-inflammatory subunits *via* their free functionalities suitable for linkage.

From carboxylic acids of steroid subunits represented by the structures **A1** to **A4** and **A6**, which are prepared as described in the literature (Suzuki, T. et al, *Chem. Soc., Perkin Trans. 1* **1998**, 3831-3836), (McLean, H. M. et al, *J. Pharm. Sci.* **1994**, *83*, 476-480), (Little, R. J. et al, *Pharm. Res.* **1999**, *16*, 961-967), (Kertesz D. J. et al, *J. Org. Chem.* **1986**, *51*, 2315-2328), (Bodor N. S. *US Patent 4,710,495*, **1987**), a compound of the general formula I can be prepared, where the activation with carboxydiimide and benzotriazole (HOBT) in anhydrous dichloromethane in the presence of a base such as triethylamine at room temperature in a flow of argon is used for the formation of an amide bond (Scheme 1).



Scheme 1

When the linking of macrolide subunits to the steroid subunits takes place *via* an ester bond, the synthesis is performed *via* the macrolide intermediate M7.



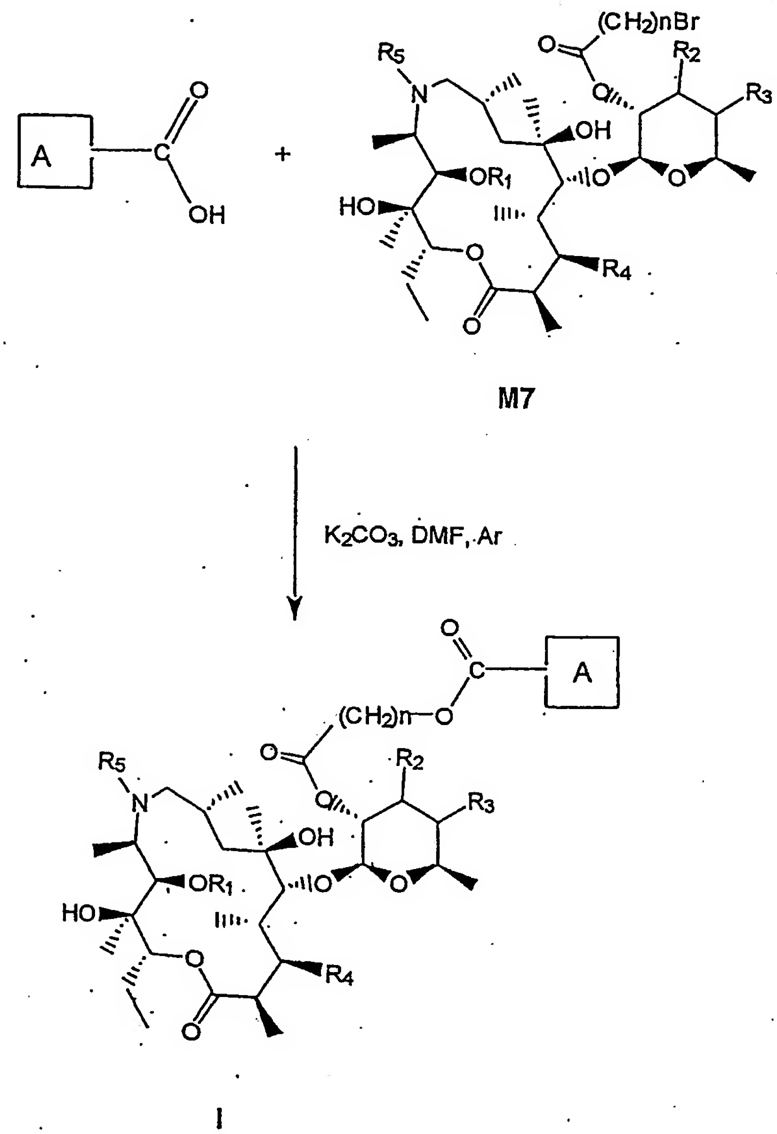
M7

Scheme 2

Esterification in position 2' of the macrolide can be performed by the reaction with a halogen-substituted acid in dry dichloromethane in the presence of pivaloyl chloride, triethylamine and dimethylaminopyridine (DMAP), thus forming intermediates **M7** for linking with carboxylic acids of the subunit **A** (Scheme 2).

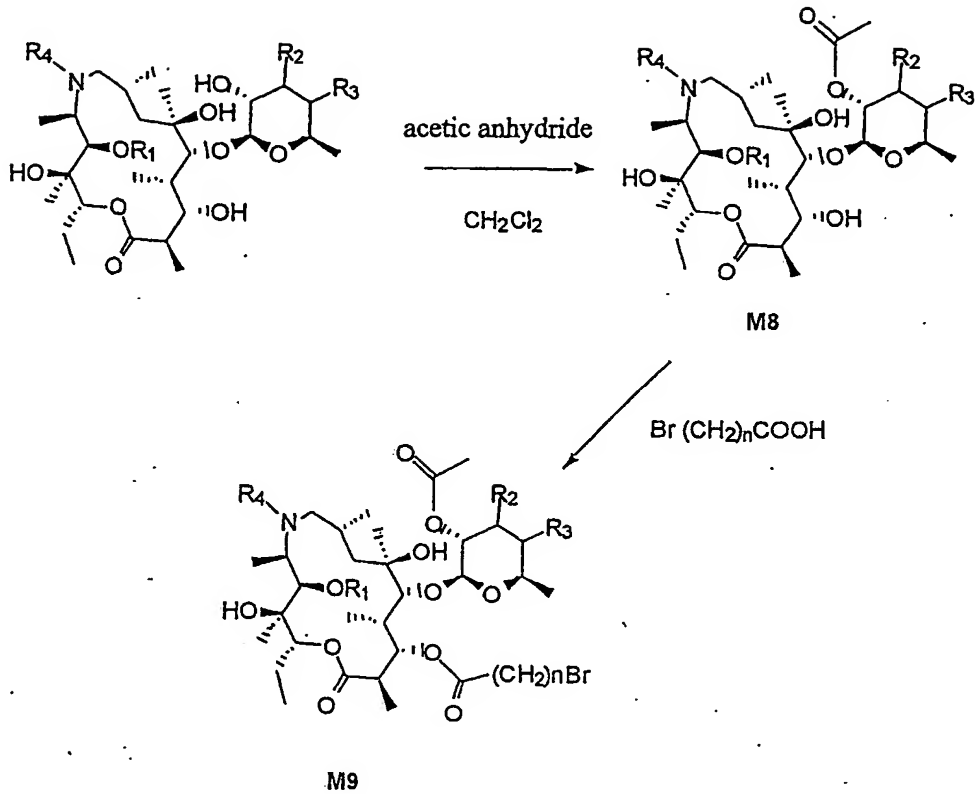
Such an intermediate can further react with the carboxylic functionality of subunit **A** in case of a steroid subunit such as represented by the structures **A1** to **A4** and **A6**.

The reaction is performed in dry DMF in the presence of a base such as potassium carbonate (K_2CO_3) in a flow of argon, yielding a potassium salt of the acid, which in the reaction with the macrolide intermediate gives a compound I of the present invention (Scheme 3).



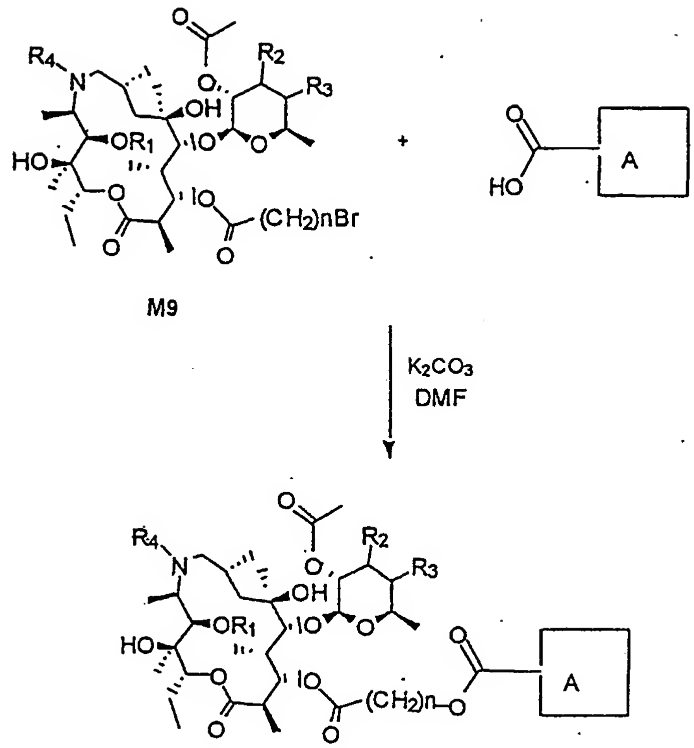
Scheme 3

When the macrolide subunit means M2 (a macrolide free of cladinose in position 3), it is also possible to perform the coupling with an anti-inflammatory subunit A *via* an ester bond, whereat the preparation of intermediates M8 and M9 is necessary (Scheme 4).



Scheme 4

Esterification with the carboxylic group of subunit A occurs selectively due to the protected 2' hydroxyl group of macrolide M9, which is also reactive.

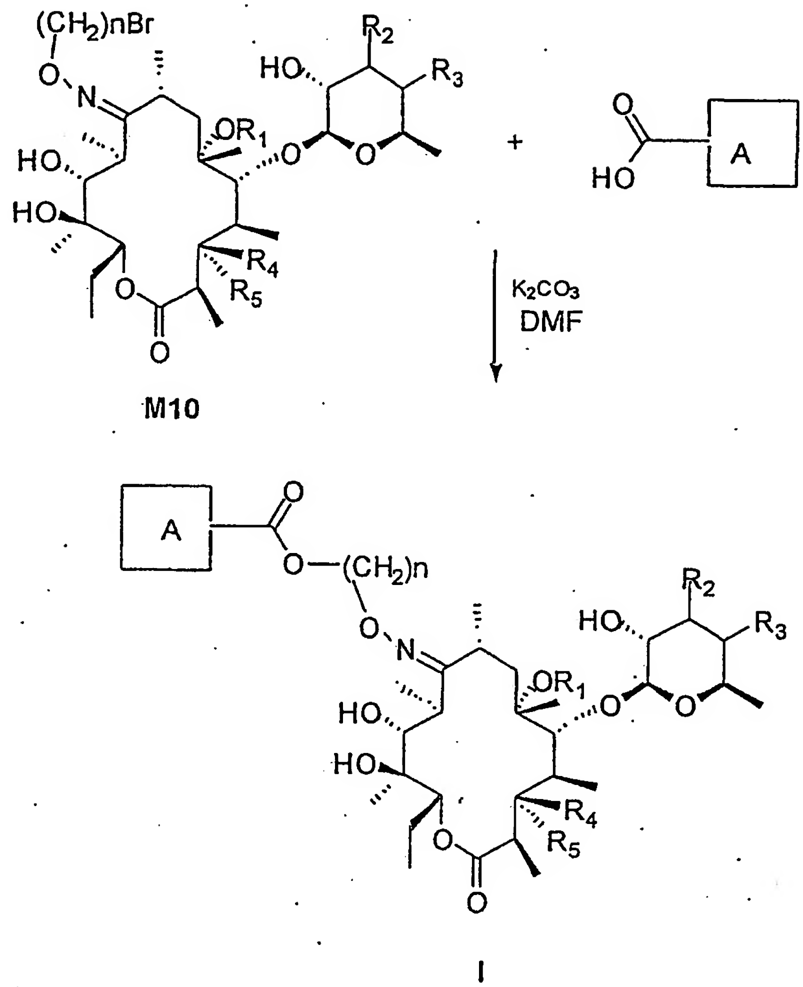


M9

I

Scheme 5

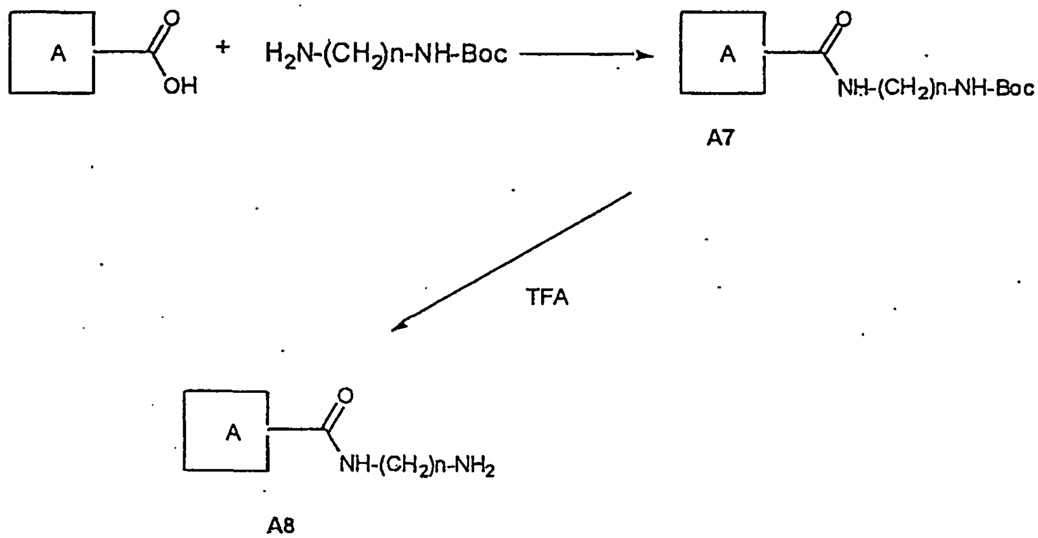
The synthesis of a compound of the structure I from a macrolide subunit indicated by **M1** is performed from an intermediate, whose synthesis is described in Agouridas C., *J. Med. Chem.* **1998,** *41,* 4080-4100, in the manner and by the use of reagents described therein. From said intermediate **M10** a compound of the structure I is synthesized by the reaction with an anti-inflammatory subunit **A** bearing a carboxylic functionality by the use of potassium carbonate in dry DMF at room temperature (Scheme 6).



Scheme 6

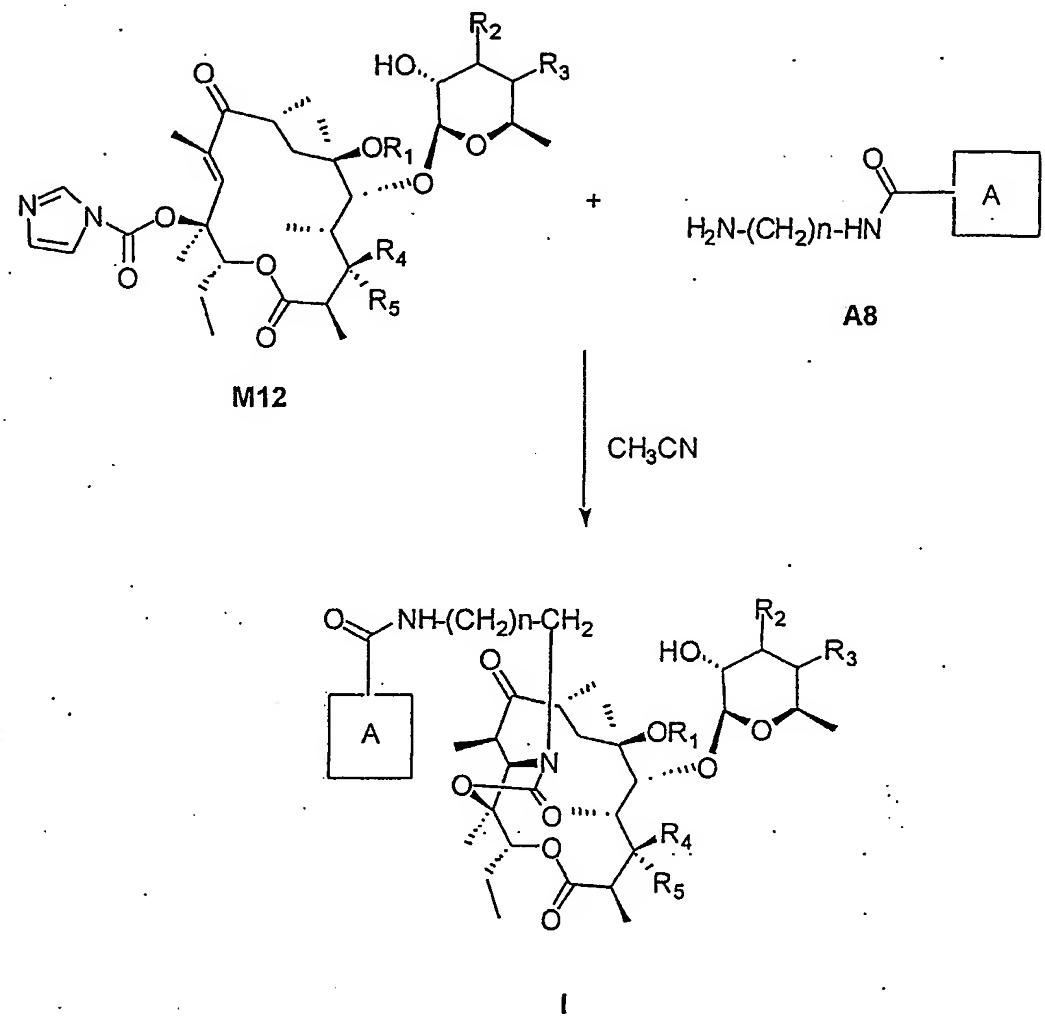
The compounds of the general structure I comprising a compound **M3** as the macrolide unit are synthesized by linking a modified anti-inflammatory unit **A8** with a macrolide **M3**, which is prepared according to the already mentioned method (Agouridas C., *J. Med. Chem.* **1998**, *41*, 4080-4100). The anti-inflammatory intermediate **A8** is prepared from an acid of the anti-inflammatory compound and a corresponding protected diamine (Boc-protection only from one side) in the presence of hidroxybenzotriazole and EDC in a suitable solvent, preferably dichloromethane or DMF. After obtaining the corresponding amide **A7**, a deprotection of the terminal

amino group is performed by the use of TFA in dichloromethane at room temperature (Scheme 7).



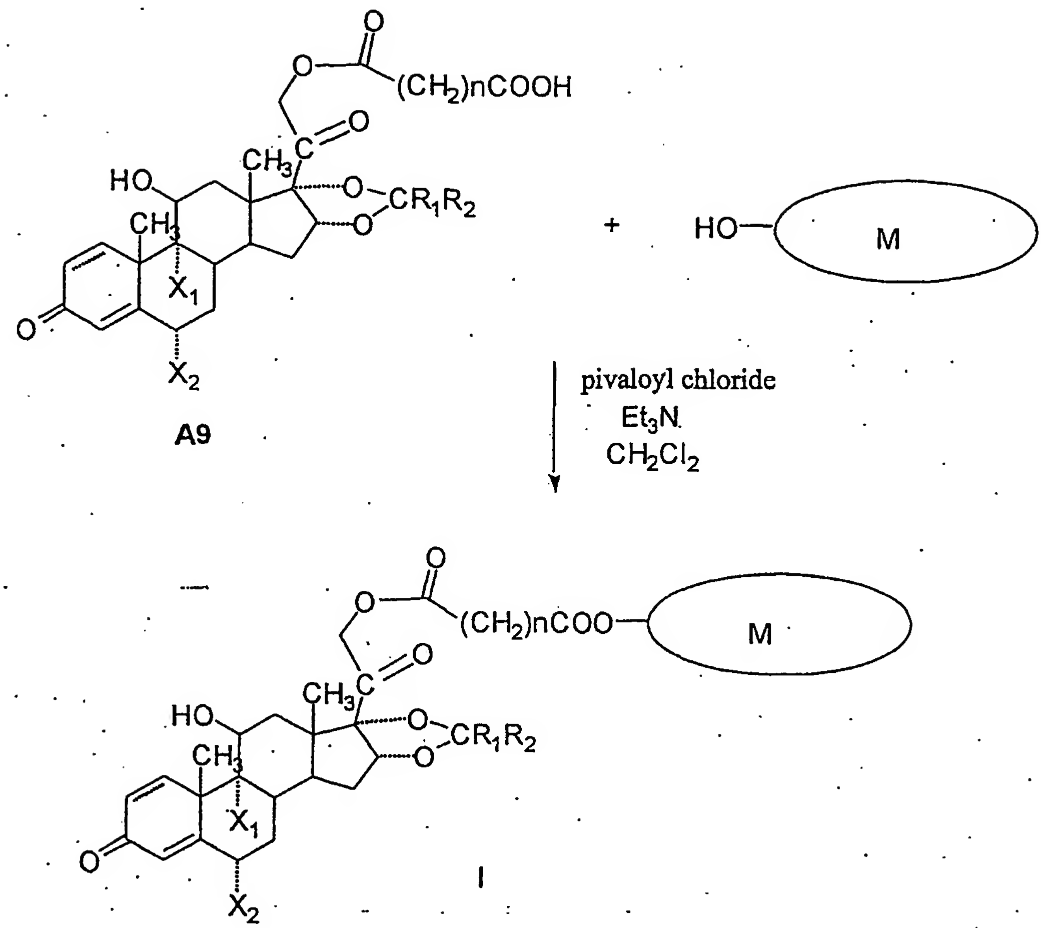
Scheme 7

The intermediate obtained according to the Scheme 7 is reacted in acetonitrile in a flow of nitrogen with a macrolide subunit **M12**, which is activated by carboxydiimide and comprises protected hydroxyl groups in positions 2' 4'' (Scheme 8).



Scheme 8

If the steroid subunit is described as indicated for the general structure **A5**, wherein all groups and radicals have the meanings as described in the above-mentioned definitions, the coupling reaction with the macrolide group is performed by the esterification of the intermediate **A9** obtained according to the literature (HU 55409) and of the macrolide hydroxyl group (Scheme 9).



Scheme 9

A further object of the present invention relates to the use of compounds of the general structure I as anti-inflammmatory, anti-anaphylactic and immunomodulating agents, which, depending on the inflammation site, can be administered in different ways such as percutaneously, orally, buccally, rectally, parenterally or by inhalation when a topical application within the respiratory tract is intended.

A further object of the present invention relates to the preparation of such pharmaceutical forms of compounds to achieve the optimal bioavailability of the active compound I. For percutaneous administration the compound I can be prepared

in a form of an ointment or a cream, a gel or a lotion. Ointments, creams and gels can be formulated by the use of a water or oil base under the addition of an appropriate emulgator or gelling agent, when a gel form is formulated. The formulation is especially significant for respiratory inhalation, wherein the compound I can be in the form of an aerosol under pressure. For all forms of aerosol formulations it is recommended to micronise the compound I, which has been previously homogenised in lactose, glucose, higher fatty acids, sodium salt of dioctylsulfosuccinic acid or, most preferably, in carboxymethyl cellulose, in order to achieve the size of 5 μm for the greatest number of particles. For the inhalation formulation the aerosol can be mixed with a propellant serving for spraying the active substance.

The compound I for inhalation application can be applied in the form of a dry powder with micronised particles.

The compound can also be incorporated in a formulation for treating Crohn's disease, where it can be administered orally or rectally. The formulation for oral administration must be formulated so as to enable the bioavailability of the compound in the inflammation part of the intestine. This can be achieved by different combinationa of delayed release formulations. The compound I can also be used in the treatment of Crohn's disease and intestine inflammation disease if the compound is applied in the form of a clyster, wherefor a suitable formulation can be used.

The appropriate preparations of the compounds that are the object of the present invention can be used in the prophylaxis or treatment of different diseases and pathological inflammatory conditions including asthma, chronic obstructive pulmonary disease, inflammatory nasal diseases such as allergic rhinitis, nasal polyps, intestinal diseases such as Crohn's disease, colitis, intestine inflammation, ulcerative colitis, dermatological inflammations such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis, conjunctivitis and rheumatoid arthritis.

The therapeutic effect of the compounds of the present invention was determined in the following *in vitro* and *in vivo* experiments.

Assay of binding to the human glucocorticoid receptor

The gene for alpha isoform of human glucocorticoid receptor was cloned by reverse polymerase chain reaction. The total RNA was isolated from human peripheral blood lymphocites according to the instructions of the manufacturer (Qiagen), transcripted into cDNA with AMV reverse transcriptase (Roche) and the gene was multiplied by specific primers

1) 5' ATATGGATCCCTGATGGACTCCAAAGAATCATTAACTCC3'
2) 5' ATATCTCGAGGGCAGTCACTTTTGATGAAACAGAAG3'

The obtained reaction product was cloned into XhoI/BamHI site of Bluescript KS plasmid (Stratagene), subjected to sequencing by dideoxy fluorescent method with M13 and M13rev primers (Mycrosynth) and then it was cloned into XhoI/BamHI site of pcDNA3.1 hygro(+)plasmid (Invitrogen). 1 x 10^5 COS-1 cells were seeded onto a 12-well plate (Falcon) in DMEM medium (Life Technologies) with 10 % FBS (Biowhitaker) and cultivated up to a 70 % confluence at 37 °C in an atmosphere with 5 % CO_2. The medium was removed and 1 μg of DNA, 7 μl of PLUS reagent and 2 μl of Lipofectamine (Life Technologies) in 500 μl DMEM were added per well. The cells were incubated at 37 °C in an atmosphere with 5 % CO_2 and after 5 hours the same volume of 20 % FBS/DMEM was added. After 24 hours the medium was completely changed. 48 hours after the transfection, the test compounds in different concentrations and 24 nM [^{3}H] dexamethasone (Pharmacia) in DMEM medium were added. The cells were incubated for 90 minutes at 37 °C in an atmosphere with 5 % CO_2, washed three times with PBS buffer (Sigma), cooled to 4 °C (pH = 7.4) and then lyzed in Tris buffer (pH = 8.0) (Sigma) with 0.2 % SDS (Sigma). After the addition of UltimaGold XR (Packard) scintillation liquid, the residual radioactivity was read in a Tricarb (Packard) β-scintillation counter.

Compounds **9, 10** and **27** are able to compete with radioactive dexamethasone in the binding site on the glucocorticoid receptor.

Assay of steroid introduction into cells

CHO and COS-1 cells were cultivated up to confluence in 75 cm^2 flasks in Hamm F 12 medium (Life Technologies) with 10 % FBS (CHO) or in DMEM medium with 10 % FBS (COS-1). 1μM of radioactive compound **10** with total 2 μCi activity was added onto the cells and it was incubated for 90 minutes at 37 °C in an atmosphere with 5 % CO_2. The cell supernatant was collected, the cells were lysed and then the radioactivity in the cell lysate as well as in the cell supernatant was read. The compound 10 was able to accumulate in the cells in a greater concentration than in the supernatant.

Assay of inhibition of mouse T-cell hybridoma 13 proliferation as a result of apoptose induction

In a 96-well plate triplicates of test steroid dilution in RPMI medium (Imunološki zavod) with 10 % PBS were performed. To the solutions of compounds 20 000 cells per well were added and incubated overnight at 37 °C in an atmosphere with 5 % CO_2, then 1 μCi of [^{3}H] thymidine (Pharmacia) was added and it was incubated for additional 3 hours. The cells were harvested by sucking over GF/C filter (Packard). Onto each well 30 μl of Microscynt O scintillation liquid (Packard) were added and the incorporated radioactivity was measured on a β-scintillation counter (Packard). The specifity of apoptose induction by glucocorticoids was proven by antagonising the proliferation inhibition with mifepristone (Sigma).

Compounds **8, 9, 10** and **27** demonstrated an inhibition of cell hybridoma 13 proliferation.

Assay of inhibition of interleukin-2 production

Onto a 96-well plate (Nunc) 15 ng of 2C11 antibodies (Pharmingen) per well were added and left to adsorb in PBS buffer (pH = 7.4) overnight at 4 °C. PBS was removed, the plate was washed with RPMI medium and then 50 000 cells per well were added and incubated in the medium with and without a dilution of the test compounds. The concentration of IL-2 in the supernatant was measured by ELISA specific for mouse IL-2 (R&D Systems).

The compounds **9**, **10** and **27** demonstrate an inhibition of interleukin-2 production induced by the stimulation *via* CD3 receptor.

Table 2

Compound	Binding to the glucocorticoid receptor	Induction of H13 cells apoptose	Inhibition of IL-2 synthesis
5	ND	-	-
8	+	+	+
9	+	+	+
10	+	+	+
11	ND	-	-
27	+	+	+
dexamethasone	+	+	+

ND - not determined

Model of croton oil-induced ear edema

Male Sprague Dawley rats with body weight of 200-250 g were randomly divided into groups, marked and the inital ear thickness was measured with a digital caliper.

To the control group 50 μl of solvent (acetone, Kemika) per ear were applied. In the same manner also the test compound in a dose of 1 mg/ear or the standard (1 mg/ear of dexamethasone, Krka) dissolved in acetone were applied. Thirty minutes later an ear edema was induced with 20 % croton oil (Sigma). The maximum intensity of the inflammation was reached five hours after the application of croton oil. The percentage of the ear edema inhibiton was determined by compariing the ears of the treated animals and of the control ones. In this model the compound **10** was tested, which demonstrated a similar activity as the tested standard.

Model of lung eosinophilia in mice

Male Balb/C mice with a body weight of 20-25 g were randomly divided into groups. They were sensibilized by an i.p. injection of ovalbumine (OVA, Sigma) on zero day and on the fourteenth day. On the twentieth day the mice were subjected to a provocative test by i.n. application of OVA (positive control or test groups) or PBS (negative control). 48 hours after i.n. aplication of OVA, the animals were anesthetized and the lungs were rinsed with 1 ml of PBS. The cells were separated on Cytospin 3 cytocentrifuge (Shandon). The cells were stained in Diff-Quick (Dade) and the percentage of eozinophiles was determined by differential counting of at least 100 cells.

Fluticasone and beclomethasone were used as standard substances under positive and negative control.

The compounds were administered daily i.n. or i.p. in different doses 2 days before provocative test and up to the completion of the test.

Compounds **8**, **9** and **10** statistically significantly (t-test, $p<0.05$) reduced the number of eosinophiles in the lung rinse with regard to the positive control.

Influence of compounds on the thymus weight

Male Sprague Dawley rats with a body weight of 200 g were randomly divided into groups of six animals. To anaesthetized animals sterilized weighed pellets of filter paper were implanted s.c. dorsally. The pellets in the control group were impregnated with acetone, whereas in the test groups they were impregnated either with the standard (prednisolone, Sigma) or with the compound **10**. After 7 days the animals were put to sleep and their thymuses were isolated and weighed. The systemic effects were estimated by comparing the thymus weight in the test and control groups.

The standard statistically significantly reduced the thymus weights with regard to the control, while the compound **10** did not affect the thymus weights.

Preparation processes with Examples

The present invention is illustrated but in no way limited by the following Examples.

Example 1

Intermediate **M11**, wherein R_4 represents a cladinose group (9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A)

To a solution of 9-deoxo-9a-aza-9a-(β-cianoethyl)-9a-homoerythromycin A (3 g; 3.8 mmole) in ethanol (100 ml), 500 mg of PtO_2 were added. The reaction was performed in an autoclave during 2 days under the pressure of 40 bar. Subsequently, the reaction mixture was filtered and ethanol was evaporated on a rotary evaporator. The residue was purified on a silica gel column (eluant: CH_3OH:CH_2Cl_2:NH_4OH = 50:30:2). 700 mg of the pure product were obtained. MS(ES^+): 793 (MH^+)

Intermediate **M11**, wherein R_4 represents a hydroxyl group

The intermediate M11 was prepared according to the process descibed in Example 1 from 3-decladinosyl-9-deoxo-9a-aza-9a(β-cianoethyl)-9a-homoerythromycin A (3.5 g; 5.55 mmole). 985 mg of the product were obtained. MS (ES^+): 635 (MH^+)

Example 2

Intermediate **M7**, wherein R_4 represents a cladinose group

To a solution of 5-bromovaleric acid (1.282 g; 7.07 mmole) in dry CH_2Cl_2 (10 ml), 1 ml (7.23 mmole) of triethylamine, 868 mg (7.10 mmole) of 4-dimethyl-aminopyridine and 0.940 ml (7.63 mmole) of pivaloyl chloride were added. The solution was stirred for 2 hours at room temperature in a flow of argon and then a solution of azithromycin (2 g; 2.67 mmole) in 10 ml of dry CH_2Cl_2 was added. The reaction mixture was stirred for three days at room temperature. Subsequently, 60 ml of saturated $NaHCO_3$ solution were added to the reaction mixture and the layers were

separated. The aqueous layer was twice more extracted with 40 ml of CH_2Cl_2. The combined organic extracts were washed with a saturated NaCl solution, dried over K_2CO_3 and evaporated in a rotary evaporator. The obtained oily product was purified on a silica gel column (eluant: CH_2Cl_2:CH_3OH:NH_4OH = 90:9:1.5). 511 mg of the pure product were obtained . MS(ES^+): 912 (MH^+)

The intermediates **M7** and **M9** were prepared according to the process described in Example 2.

Intermediate M7, wherein R_4 represents a hydroxyl group.

The intermediate M7 was prepared from 3-decladynosyl azithromycin (1 g; 1.71 mmole) and 5-bromovaleric acid (929 mg; 5.13 mmole). 400 mg of the product were obtained. MS(ES^+): 754 (MH^+)

Intermediate **M9**

The intermediate M9 was prepared from 2'-acetyl-3-decladynosyl azithromycin (1.1 g; 1.70 mmole) and 5-bromovaleric acid (921 mg; 5.09 mmole). 329 mg of the product were obtained. MS(ES^+): 795 (MH^+)

Example 3

Compound 1

To a suspension of 9α-chloro-6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (100 mg; 0.29 mmole) in dry CH_2Cl_2 (5 ml) cooled to 0°C under argon, 0.380 ml (2.73 mmole) of triethylamine, 80 mg (0.59 mmole) of 1-hydroxybenzotriazole, 230 mg (0.29 mmole) of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A and 235 mg (1.23 mmole) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride were added. The reaction mixture was stirred for 24 hours at room temperature in a flow of argon, then

evaporated to a smaller volume on a rotary evaporator and purified on a silica gel column. (eluant: $CHCl_3$:CH_3OH:NH_4OH = 6:1:0.1). 224 mg of white crystals were obtained (Table 1).

Compounds **2-12** were prepared from 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A and the corresponding steroid acids according to the process described in Example 3 and stated in Table 1.

Compound 2

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 11β,17α-dihydroxyandrosta-1,4-diene-3-one-17β-carboxylic acid (100 mg; 0.29 mmole), white crystals (285 mg) were obtained.

Compound 3

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (197 mg; 0.25 mmole) and 11β-hydroxy-17α-metoxyandrost-4-ene-3-one-17β-carboxylic acid (90 mg; 0.25 mmole), white crystals (115 mg) were obtained.

Compound 4

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (174 mg; 0.22 mmole) and 9α-fluoro-11β-hydroxy-16α-methyl-androsta-1,4-diene-3-one-17β-carboxylic acid (80 mg; 0.22 mmole), white crystals (224 mg) were obtained.

Compound 5

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 11β-hydroxyandrost-4-ene-3-one-17β-carboxylic acid (96 mg; 0.29 mmole), white crystals (238 mg) were obtained.

Compound 6

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 9α-fluoro-11β,17α-dihydroxyandrosta-1,4-diene-3-one-17β-carboxylic acid (106 mg; 0.29 mmole), white crystals (225 mg) were obtained.

Compound **7**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 6α-fluoro-11β,17α-dihydroxy-16α-methyl-androsta-1,4-diene-3-one-17β-carboxylic acid (110 mg; 0.29 mmole), white crystals (107 mg) were obtained.

Compound **8**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 11β,17α-dihydroxyandrost-4-ene-3-one-17β-carboxylic acid (100 mg; 0.29 mmole), white crystals (75 mg) were obtained.

Compound **9**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 6α,9α-difluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-diene-3-one-17β-carboxylic acid (115 mg; 0.29 mmole), white crystals (258 mg) were obtained.

Compound **10**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 9α-fluoro-11β,17α-dihydroxy-16α-methylandrosta-1,4-diene-3-one-17β-carboxylic acid (110 mg; 0.29 mmole), white crystals (224 mg) were obtained.

Compound **11**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (197 mg; 0.24 mmole) and 9α-chloro-11β,17α-dihydroxy-16α-methylandrosta-1,4-diene-3-one-17β-carboxylic acid (96 mg; 0.24 mmole), white crystals (170 mg) were obtained.

Compound **12**

By a reaction of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (230 mg; 0.29 mmole) and 17α-hydroxyandrost-4-ene-3,11-dione-17β-carboxylic acid (100 mg; 0.29 mmole), white crystals (247 mg) were obtained.

Example 4

Compound **13**

A mixture of 6α,9α-difluoro-11β,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid-16,17-acetonide (104 mg; 0.24 mmole), diizopropylethylamine (45 ml, 0.26 mmole), 1-hidroxybenzotriazole (65 mg; 0.48 mmole), 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (190 mg; 0.24 mmole) and 1-(3-dimethyl-aminopropyl)-3-ethyl-carbodiimide hydrochloride (184 mg; 0.96 mmole) in dry DMF (10 ml) was heated under reflux while stirring at 100 °C in an argon atmosphere. Subsequently, the reaction mixture was cooled and evaporated on a rotary evaporator. The residue was purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH = 6:1:0.1). 31 mg of the pure product were obtained (Table 1).

Compound **14**

Compound 14 was prepared according to the process described in Example 4 from 6α,9α-difluoro-11β,16α,17α-trihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid-16,17-acetonide (104 mg; 0.24 mmole) and 3-decladinosyl-9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A (150 mg; 0,24 mmole). 60 mg of the product were obtained (Table 1).

Example 5

Compound **15**

To a suspension of 9α-chloro-6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (110 mg; 0.27 mmole) in dry CH_2Cl_2 (5 ml) cooled to 0 °C in a flow of argon, 0.348 ml (2.5 mmole) of triethylamine, 73 mg (0.54 mmole) of 1-hydroxybenzotriazole, 169 mg (0.27 mmole) of 3-decladinosyl-9-deoxo-9a-aza-9a-(-(γ-aminopropyl)-9a-homoerythromycin A and 215 mg (1.12 mmole) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride were added. The reaction mixture was stirred for 24 hours at room temperature, evaporated to a smaller volume on a rotary evaporator and purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH = 6:1:0.1). 235 mg of white crystals were obtained (Table 1).

Compounds **16-19** were prepared according to the process described in Example 5 and stated in Table 1.

Compound **16**

By a reaction of 6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (90 mg; 0.24 mmole) and 3-decladinosyl-9-deoxo-9a-aza-9a-(-(γ-aminopropyl)-9a-homoerythromycin A (150 mg; 0.24 mmole), white crystals (138 mg) were obtained.

Compound **17**

By a reaction of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (94 mg; 0.24 mmole) and 3-decladinosyl-9-deoxo-9a-aza-9a-(-(γ-aminopropyl)-9a-homoerythromycin A (150 mg; 0.24 mmole), white crystals (163 mg) were obtained.

Compound **18**

By a reaction of 11β,17α-dihydroxyandrost-4-ene-3-one-17β-carboxylic acid (84 mg; 0.24 mmole) and 3-decladinosyl-9-deoxo-9a-aza-9a-(-(γ-aminopropyl)-9a-homo-erythromycin A (150 mg; 0.24 mmole), white crystals (112 mg) were obtained.

Compound **19**

By a reaction of 9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (110 mg; 0.29 mmole) and 3-decladinosyl-9-deoxo-9a-aza-9a-(-(γ-aminopropyl)-9a-homoerythromycin A (185 mg; 0.29 mmole), white crystals (155 mg) were obtained.

Example 6

Compound **20**

To a suspension of stereoisomeric acid (20 *R,S*)-11β,17,20-trihydroxy-3-oxoandrosta-1,4-diene-21-carboxylic acid (200 mg; 0.53 mmole) in dry CH_2Cl_2 (5 ml) under argon, 0.760 ml of triethylamine, 160 mg (1.2 mmole) of 1-hydroxybenzotriazole, 460 mg (0.58 mmole) of 9-deoxo-9a-aza-9a-(γ-aminopropyl)-9a-homoerythromycin A and 470 mg (2.45 mmole) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride were added. The reaction mixture was stirred for 24 hours at room temperature, then evaporated to a smaller volume on a rotary evaporator and purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH = 6:1:0.1). 405 mg of the product were obtained (Table 1).

Example 7

Compound **21**

To a solution of 9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (135 mg; 0.35 mmole) in dry DMF (3 ml), potassium carbonate (49 mg; 0.35 mmole) was added. The reaction mixture was stirred at 0°C in a flow of argon and then a solution of 311 mg (0.39 mmole) of the intermediate **M9** in 4 ml of

dry DMF was added. After stirring for 5 days at room temperature, DMF was evaporated on a rotary evaporator and the residue was purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH =10:1:0.1). 53 mg of the pure product were obtained (Table 1).

Example 8

Compound **22**

To a solution of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (100 mg; 0.25 mmole) in dry DMF (3 ml), potassium carbonate (35 mg; 0.25 mmole) was added. The reaction mixture was stirred at 0°C in a flow of argon and then a solution of 252 mg (0.28 mmole) of the intermediate **M7**, wherein R_4 represents cladinose, in 4 ml of dry DMF was added. After stirring for 2 days at room temperature, DMF was evaporated on a rotary evaporator and the residue was purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH = 12:1:0.1). 42 mg of the pure product were obtained (Table 1).

Compounds **23** and **24** were prepared according to the process described in Example 8 and stated in Table 1.

Compound **23**

By a reaction of 9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (99 mg; 0.26 mmole) and 285 mg (0.31 mmole) of intermediate **M7**, wherein R_4 represents cladinose, white crystals (42 mg) were obtained.

Compound **24**

By a reaction of 9α-chloro-6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (81 mg; 0.20 mmole) and 222 mg (0.24 mmole) of intermediate **M7**, wherein R_4 represents cladinose, white crystals (54 mg) were obtained (Table 1).

Example 9

Compound **25**

To a solution of 9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (83 mg; 0.22 mmole) in dry DMF (3 ml), potassium carbonate (30 mg; 0.22 mmole) was added. The reaction mixture was stirred at 0°C in a flow of argon and then a solution of 182 mg (0.24 mmole) of intermediate M7, wherein R_4 represents a hydroxyl group, in 4 ml of dry DMF was added. After stirring for 24 hours at room temperature, DMF was evaporated on a rotary evaporator and the residue was purified on a silica gel column (eluant: $CHCl_3$:CH_3OH:NH_4OH = 10:1:0.1). 57 mg of the pure product were obtained.

Compounds **26** and **27** were prepared according to the process described in Example 9 and stated in Table 1.

Compound **26**

By a reaction of 6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (85 mg; 0.22 mmole) and 225 mg (0.25 mmole) of intermediate M7, wherein R_4 represents a hydroxyl group, white crystals (20 mg) were obtained.

Compound **27**

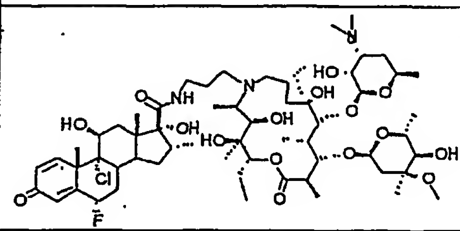
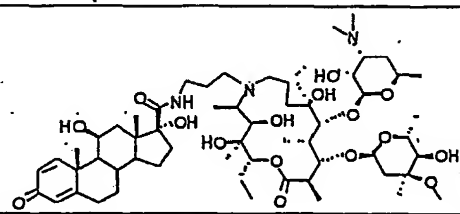
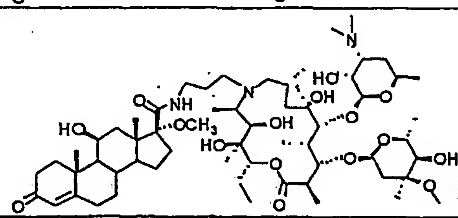
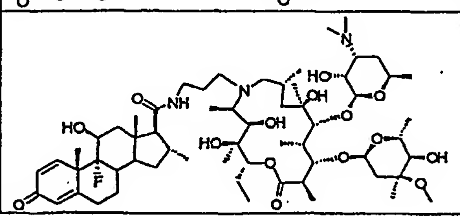
By a reaction of 9α-chloro-6α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (100 mg; 0.24 mmole) and 200 mg (0.26 mmole) of intermediate M7, wherein R_4 represents a hydroxyl group, white crystals (59 mg) were obtained.

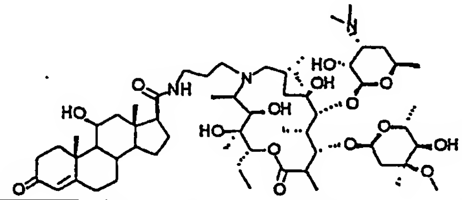
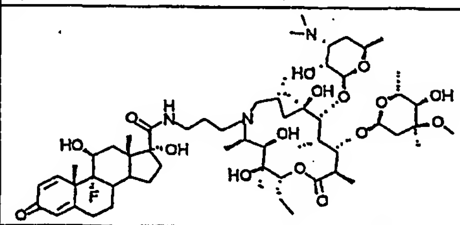
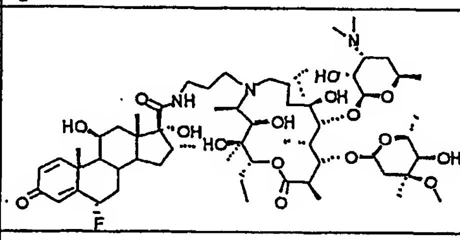
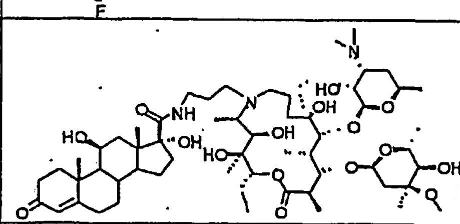
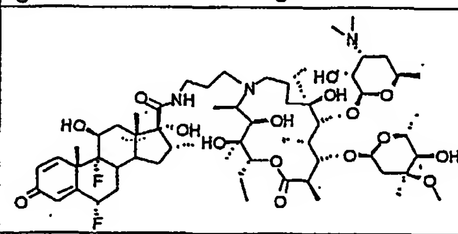
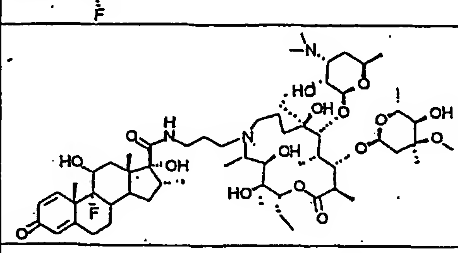
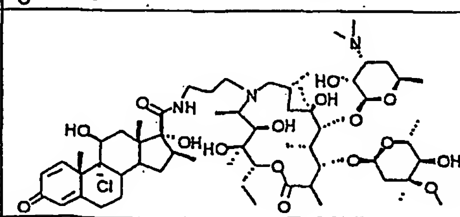
Example **10**

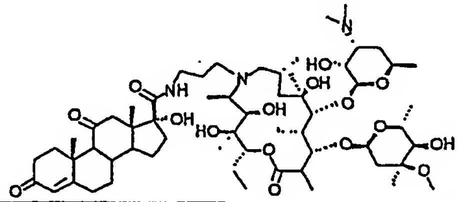
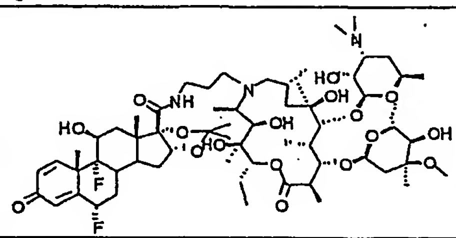
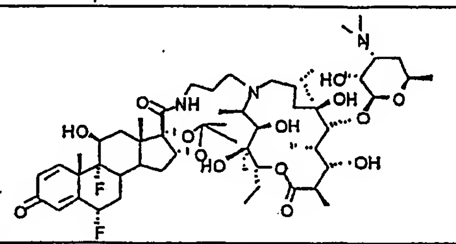
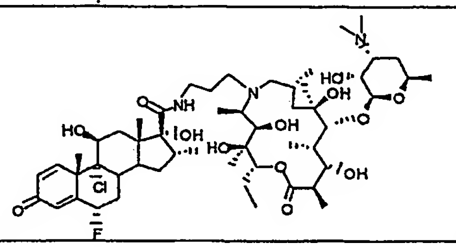
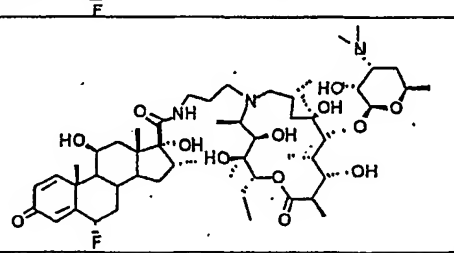
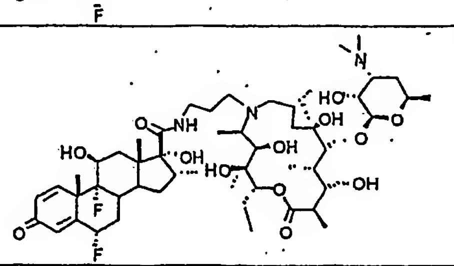
Compound **28**

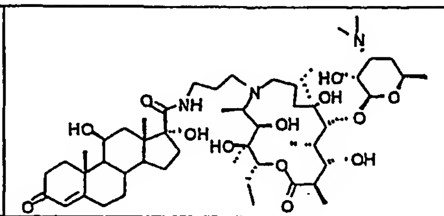
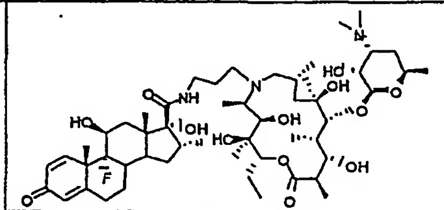
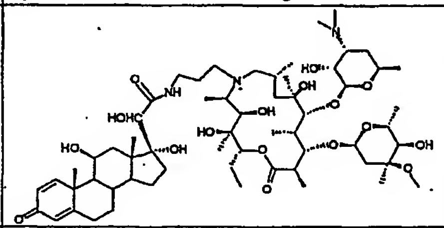
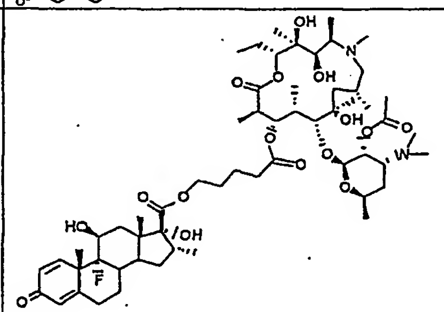
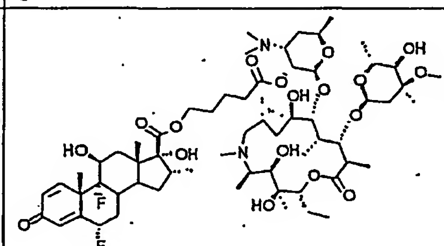
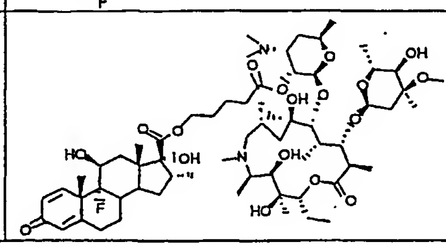
To a solution of 9α-fluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (80 mg; 0.21 mmole) in dry DMF (3 ml), potassium carbonate (30 mg; 0.21 mmole) was added. The reaction mixture was stirred for one hour at room temperature in a flow of argon and then a solution of 163 mg (0.23 mmole) of 3-O-decladinosyl-6-O-methyl-3-oxoerythromycin-9-O-(2-bromoethyl)oxime in 3 ml of dry DMF was added. The reaction mixture was heated for 4 hours at 100 °C. Then it was cooled to room temperature and 40 ml of ethyl-acetate and water (1:1) were added. The organic layer was separated, washed with water and dried over anhydrous potassium carbonate. The residue was purified on a silica gel column with a solvent system chlorophorm:methanol:ammonia = 10:1:0.1. 160 mg of white crystals were obtained (Table 1).

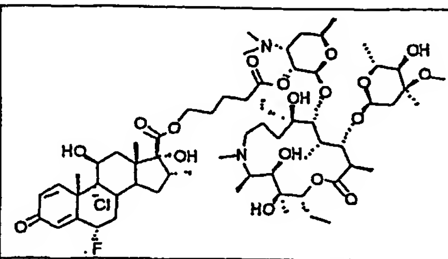
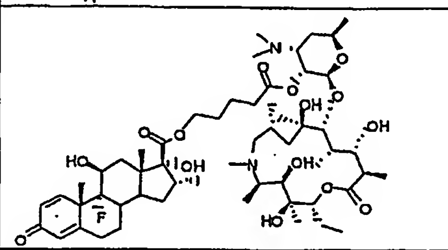
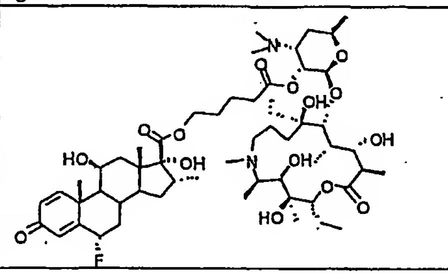
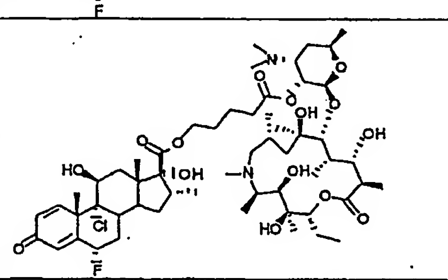
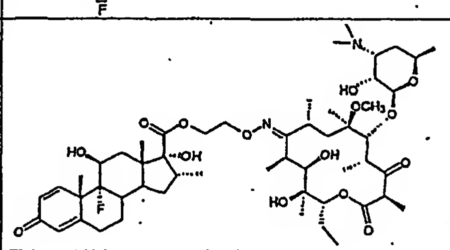
Table 1

Comp.	Structure	Molecular formula	M.p. (°C)	MH^+ (ES^+)
1		$C_{61}H_{101}ClFN_3O_{16}$	194-202	1187
2		$C_{60}H_{101}N_3O_{16}$		1121
3		$C_{61}H_{105}N_3O_{16}$	-	1137
4		$C_{61}H_{102}FN_3O_{15}$		1137

5		$C_{60}H_{103}N_3O_{15}$	-	1106
6		$C_{60}H_{100}FN_3O_{16}$	-	1139
7		$C_{61}H_{102}FN_3O_{16}$	175-178	1153
8		$C_{60}H_{103}N_3O_{16}$	144	1123
9		$C_{61}H_{101}F_2N_3O_{16}$	169	1171
10		$C_{61}H_{102}FN_3O_{16}$	170-175	1153
11		$C_{61}H_{102}ClN_3O_{16}$	-	1169

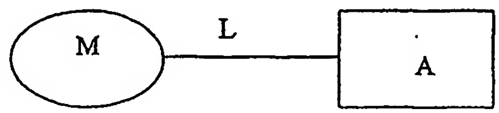
12		$C_{60}H_{101}N_3O_{16}$	-	1121
13		$C_{63}H_{103}F_2N_3O_{17}$	178	1212
14		$C_{55}H_{89}F_2N_3O_{14}$	-	1055
15		$C_{53}H_{87}ClFN_3O_{13}$	130-132	1086
16		$C_{53}H_{88}FN_3O_{13}$	202-204	995
17		$C_{53}H_{87}F_2N_3O_{13}$	182	1013

18		$C_{52}H_{89}N_3O_{13}$	160-161	965
19		$C_{53}H_{88}FN_3O_{13}$	260-265	995
20		$C_{61}H_{103}N_3O_{17}$		1151
21		$C_{58}H_{93}FN_2O_{16}$	174-175	1094
22		$C_{64}H_{104}F_2N_2O_{18}$	159-160	1228
23		$C_{64}H_{105}FN_2O_{18}$	161-168	1210

24		$C_{64}H_{104}ClFN_2O_{18}$	91-99	1244
25		$C_{56}H_{91}FN_2O_{15}$	170	1052
26		$C_{56}H_{91}FN_2O_{15}$	145-151	1052
27		$C_{56}H_{90}ClFN_2O_{15}$	130-132	1086
28		$C_{53}H_{83}FN_2O_{15}$	-	1007

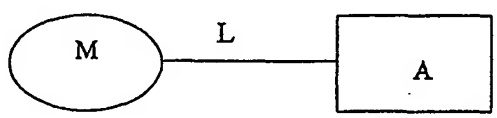
Claims

1. Compounds, their salts and solvates represented by the structure I

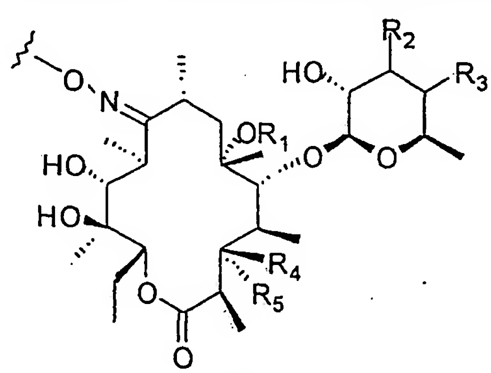


characterized in that **M** represents a macrolide subunit possessing the property of accumulation in inflammatory cells, **A** represents an anti-inflammatory subunit that can be steroid or nonsteroid and **L** represents a chain linking **M** and **A**,
and improved therapeutic effect of these compounds in the treatment of inflammation diseases and conditions.

2. Compounds, their salts and solvates represented by the structure I



characterized in that **M** represents a macrolide subunit represented by the formulas



M1

wherein

R_1 is hydrogen or a methyl group,

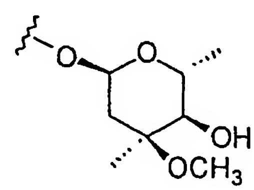
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

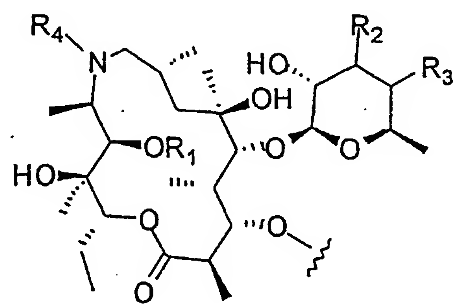
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_4 and R_5 may also together form a carbonyl group, with the proviso that R_1 is then a methyl group,



M2

wherein

R_1 is hydrogen or a methyl group,

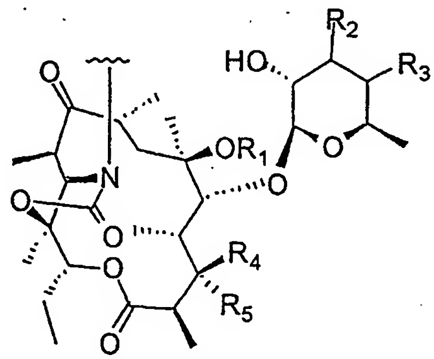
R_2 and R_3 are both hydrogen or together form a bond or

R_2 is an amino group represented by the substructure

-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group;



M3

wherein

R_1 is hydrogen or a methyl group,

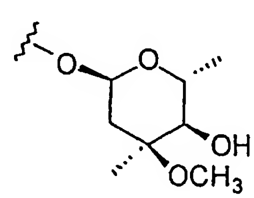
R_2 and R_3 are both hydrogen or together form a bond or

R_2 is an amino group represented by the substructure

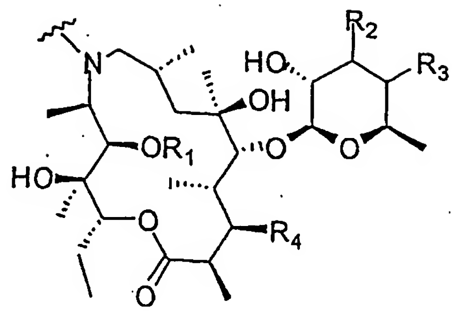
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_4 and R_5 may also together form a carbonyl group, with the proviso that R_1 is then a methyl group,



M4

wherein

R_1 is hydrogen or a methyl group,

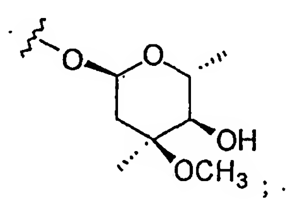
R_2 and R_3 are both hydrogen or together form a bond or

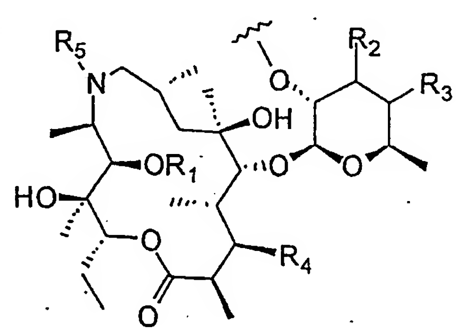
R_2 is an amino group represented by the substructure

-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure





M5

wherein

R_1 is hydrogen or a methyl group,

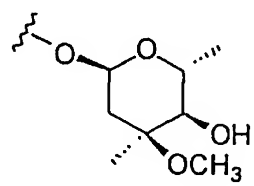
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

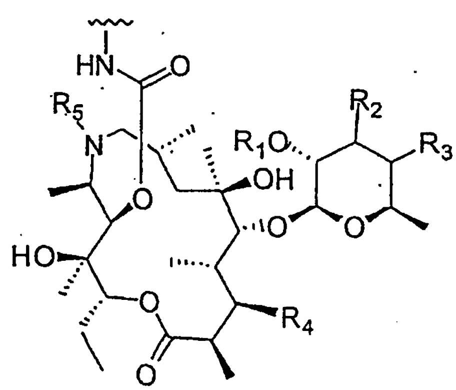
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is hydroxyl or cladinosyl group represented by the structure:



R_5 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group,



M6

wherein

R_1 is hydrogen or an acetyl group,

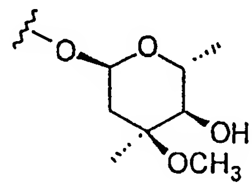
R_2 and R_3 are both hydrogen or together form a bond, or

R_2 is an amino group represented by the substructure

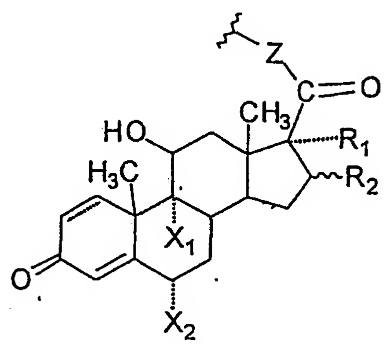
-NR'R''

wherein R' and R'' may be, independently from each other, hydrogen or any alkyl or cycloalkyl group having 1-6 carbon atoms, with the proviso that R_3 is then hydrogen,

R_4 is a hydroxyl or cladinosyl group represented by the structure



R_5 may be any alkyl group having 1-4 carbon atoms, preferably a methyl group, and A represents an anti-inflamatory subunit represented by the formulas:



A1

wherein Z represents oxygen or NH group, R_1 is hydrogen or hydroxyl or O-acyl or O-alkyl group,

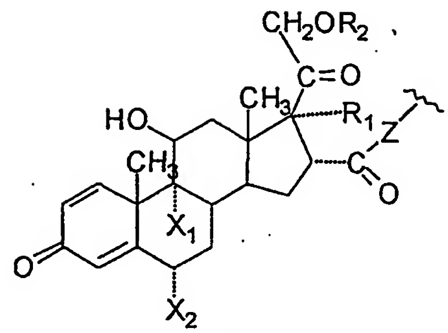
R_2 represents hydrogen or a methyl group, which may be oriented in α- or β-position,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine,

1,2-position may represent a double or single carbon-carbon bond,



A2

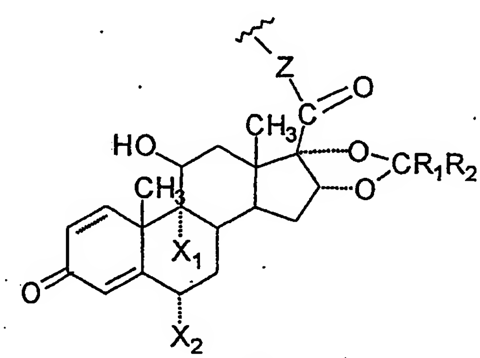
wherein Z represents oxygen or a NH group, R_1 is hydrogen or a hydroxyl or O-acyl or O-alkyl group,

R_2 represents hydrogen or an acyl group,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

whereat halogen represents fluorine, chlorine or bromine,



A3

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond, wherein Z represents oxygen or NH group,

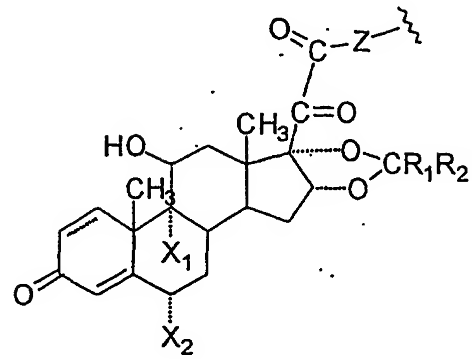
R_1 represents hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 represents hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms, with the proviso that R_1 and R_2 are not simultaneously hydrogen

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A4

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond, wherein Z represents oxygen or a NH group,

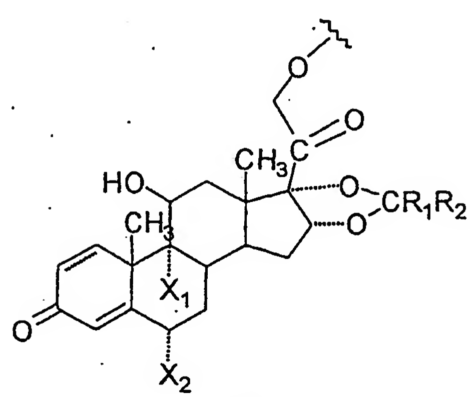
R_1 represents hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 represents hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms, with the proviso that R_1 and R_2 are not simultaneously hydrogen,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A5

or stereoisomeric forms thereof, wherein the 1,2-position represents a saturated or unsaturated double bond,

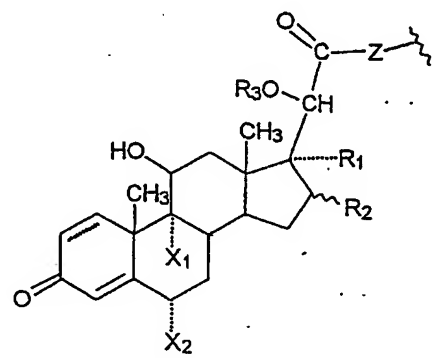
R_1 represents hydrogen, a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 represents hydrogen, a straight or branched hydrocarbon chain having 1-10 carbon atoms, with the proviso that R_1 and R_2 are not simultaneously hydrogen,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine;



A6

wherein Z represents oxygen or a NH group, R_1 is hydrogen or a hydroxyl group with a free hydrogen or a hydroxyl group or O-acyl or O-alkyl group,

R_2 represents hydrogen or a methyl group, which may be oriented in α- or β-position,

R_3 represents hydrogen or a radical of an acid having 1-4 carbon atoms,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen,

with halogen meaning fluorine, chlorine or bromine,

1,2-position may represents double or single carbon-carbon bond,

and L represents a chain with the formula

$$-CR_1R_2(CR_3R_4)_nCR_5R_6-,$$

wherein R_1, R_2, R_3, R_4, R_5, R_6 may be hydrogen, C_1-C_4 alkyl, aryl, metoxy, halogen, hydroxy or mercapto groups, wherein n is 1-10, and one or more $-CR_3R_4-$ groups may be substituted with oxygen, sulphur, an aromatic nucleus or an amino group

additionally bearing hydrogen or a C_1-C_4 alkyl or aryl group with the proviso that at least one methylene group is situated at the end of the linking L group.

3. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit **M** from structure I is represented by the general structure **M1**,
wherein
R_1 is a methyl group,
R_2 is a dimethylamino group,
with the proviso that R_3 is then hydrogen,
R_4 is cladinose,
R_4 and R_5 may also together form a carbonyl group,
and the steroid subunit of the structure I is represented by one of the structures **A1** to **A4** and **A6**,
wherein **A1** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
R_1 is a hydroxyl group which can have a free hydrogen or is additionally alkylated with an alkyl group R' having 1-4 carbon atoms, preferably a methyl group,
R_2 is hydrogen or a methyl group,
X_1 is hydrogen or fluorine,
X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
R_1 is hydrogen,
R_2 is hydrogen,
X_1 is fluorine,
X_2 is hydrogen,

wherein **A3** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A6** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is a double carbon-carbon bond,

R_1 is a hydroxyl group,

R_2 is hydrogen or a methyl group in α- or β-position, preferably in α-position,

R_3 is hydrogen,

X_1 is hydrogen, fluorine or chlorine,

X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,

wherein R_1 to R_4 are hydrogen and n is 1-10.

4. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit **M** from the structure I is represented by the general structure **M2**, wherein

R_1 is hydrogen,

R_2 is a dimethylamino group,

with the proviso that R_3 is then hydrogen,

R_4 is a methyl group,

and the steroid subunit from the structure I is represented by one of the structures **A1** to **A4** and **A6**,

wherein **A1** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is hydroxyl group, which can have a free hydrogen or is additionally alkylated with alkyl group R' having 1-4 carbon atoms, preferably methyl group,

R_2 is hydrogen or methyl group,

X_1 is hydrogen or fluorine,

X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2

wherein Z represents oxygen or a NH group,

R_1 is hydrogen,

R_2 is hydrogen,

X_1 is fluorine,

X_2 is hydrogen,

wherein **A3** is defined as in claims 1 and 2

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A6** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is double carbon-carbon bond,
R_1 is hydroxyl group,
R_2 is hydrogen or methyl group in α- or β-position, preferably in α-position,
R_3 is hydrogen,
X_1 is hydrogen, fluorine or chlorine,
X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,
wherein R_1 to R_4 are hydrogen and n is 1-10.

5. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit **M** of the structure I is represented by the general structure **M3**,
wherein
R_1 is hydrogen,
R_2 is dimethylamino group,
with the proviso that R_3 is then hydrogen,
R_4 and R_5 may together form carbonyl group,
and steroid subunit of the structure I is indicated with one of the structures **A1** to **A4** and **A6**,
wherein **A1** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
R_1 is hydroxyl group which can have a free hydrogen or is additionally alkylated with alkyl group R' having 1-4 carbon atoms, preferably methyl group,
R_2 is hydrogen or methyl group,
X_1 is hydrogen or fluorine,
X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,

R_1 is hydrogen,

R_2 is hydrogen,

X_1 is fluorine,

X_2 is hydrogen,

wherein **A3** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A6** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is a double carbon-carbon bond,

R_1 is a hydroxyl group,

R_2 is hydrogen or a methyl group in α- or β-position, preferably in α-position,

R_3 is hydrogen,

X_1 is hydrogen, fluorine or chlorine,

X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,

wherein R_1 to R_4 are hydrogen and n is 1-10.

6. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit M of the structure I is represented by the general structure **M4**, wherein

R_1 is hydrogen,

R_2 is a dimethylamino group,

with the proviso that R_3 is then hydrogen,

R_4 is a cladinose or hydroxyl group,

and the steroid subunit of the structure I is represented by one of the structures **A1** to **A4** and **A6**,

wherein **A1** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is a hydroxyl group, which can have a free hydrogen or is additionally alkylated with an alkyl group R' having 1-4 carbon atoms, preferably a methyl group,

R_2 is hydrogen or a methyl group,

X_1 is hydrogen or fluorine,

X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is hydrogen,

R_2 is hydrogen,

X_1 is fluorine,

X_2 is hydrogen,

wherein **A3** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is unsaturated,
R_1 and R_2 are methyl groups,
X_1 is fluorine,
X_2 is fluorine,

wherein **A6** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is a double carbon-carbon bond,
R_1 is a hydroxyl group,
R_2 is hydrogen or a methyl group in α- or β-position, preferably in α-position,
R_3 is hydrogen,
X_1 is hydrogen, fluorine or chlorine,
X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,
wherein R_1 to R_4 are hydrogen and n is 2-10.

7. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit **M** of the structure I is represented by the general structure **M5**, wherein
R_1 is hydrogen,
R_2 is a dimethylamino group,
with the proviso that R_3 is then hydrogen,
R_4 is a cladinose or hydroxyl group,
R_5 is a methyl group,
and the steroid subunit of the structure I is represented by one of the structures **A1** to **A4** and **A6**,
wherein **A1** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,

R_1 is a hydroxyl group, which can have a free hydrogen or is additionally alkylated with an alkyl group R' having 1-4 carbon atoms, preferably a methyl group,

R_2 is hydrogen or a methyl group,

X_1 is hydrogen or fluorine,

X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is hydrogen,

R_2 is hydrogen,

X_1 is fluorine,

X_2 is hydrogen,

wherein **A3** is defined as in claims 1 and 2

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2

wherein Z represents oxygen or a NH group,

1,2-position is unsaturated,

R_1 and R_2 are methyl groups,

X_1 is fluorine,

X_2 is fluorine,

wherein **A6** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

1,2-position is a double carbon-carbon bond,

R_1 is a hydroxyl group,

R_2 is hydrogen or a methyl group in α- or β-position, preferably in α-position,

R_3 is hydrogen,

X_1 is hydrogen, fluorine or chlorine,

X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,

wherein R_1 to R_4 are hydrogen and n is 2-10.

8. Compound and salt according to claims 1 and 2, characterized in that the macrolide subunit **M** of the structure I is represented by the general structure **M6**, wherein

R_1 is hydrogen,

R_2 is a dimethylamino group,

with the proviso that R_3 is then hydrogen,

R_4 is a cladinose or hydroxyl group,

R_5 is a methyl group,

and the steroid subunit of the structure I is represented by one of the preferred structures **A1** to **A4** and **A6**,

wherein **A1** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is a hydroxyl group, which can have a free hydrogen or is additionally alkylated with an alkyl group R' having 1-4 carbon atoms, preferably a methyl group,

R_2 is hydrogen or a methyl group,

X_1 is hydrogen or fluorine,

X_2 is hydrogen,

wherein **A2** is defined as in claims 1 and 2,

wherein Z represents oxygen or a NH group,

R_1 is hydrogen,

R_2 is hydrogen,

X_1 is fluorine,

X_2 is hydrogen,

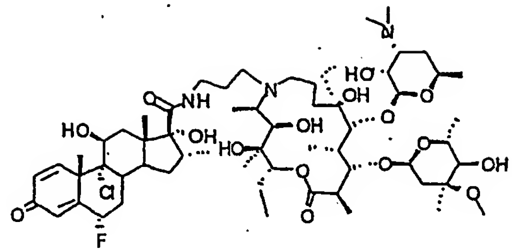
wherein **A3** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is unsaturated,
R_1 and R_2 are methyl groups,
X_1 is fluorine,
X_2 is fluorine,

wherein **A4** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is unsaturated,
R_1 and R_2 are methyl groups,
X_1 is fluorine,
X_2 is fluorine,

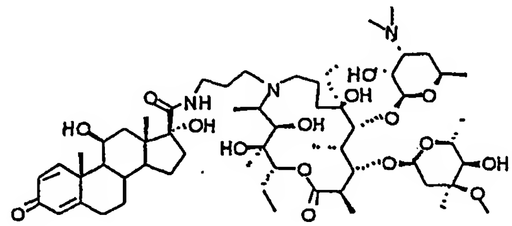
wherein **A6** is defined as in claims 1 and 2,
wherein Z represents oxygen or a NH group,
1,2-position is a double carbon-carbon bond,
R_1 is a hydroxyl group,
R_2 is hydrogen or a methyl group in α- or β-position, preferably in α-position,
R_3 is hydrogen,
X_1 is hydrogen, fluorine or chlorine,
X_2 is hydrogen or fluorine,

wherein chain **L** is indicated as defined in claim 2,
wherein R_1 to R_4 are hydrogen and n is 2-10.

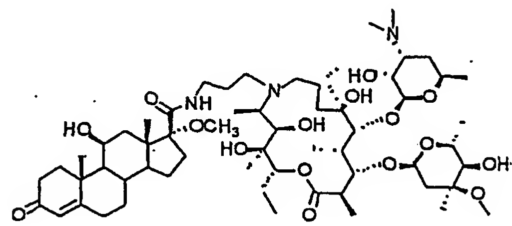
9. Compound 1 according to claims 1, 2 and 6, characterized by the formula



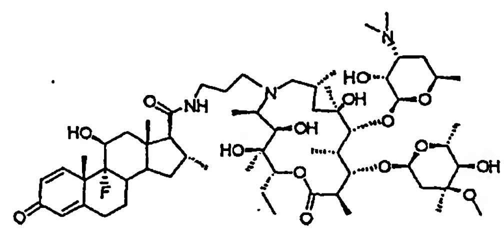
10. Compound 2 according to claims 1, 2 and 6, characterized by the formula



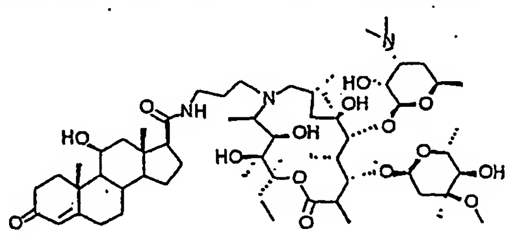
11. Compound 3 according to claims 1, 2 and 6, characterized by the formula



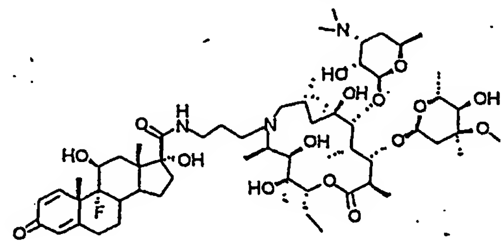
12. Compound 4 according to claims 1, 2 and 6, characterized by the formula



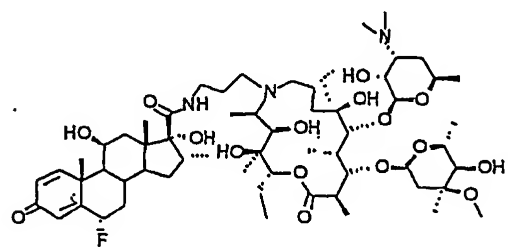
13. Compound 5 according to claims 1, 2 and 6, characterized by the formula



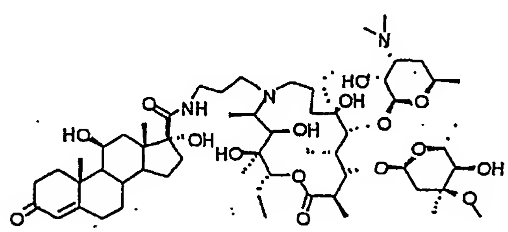
14. Compound 6 according to claims 1, 2 and 6, characterized by the formula



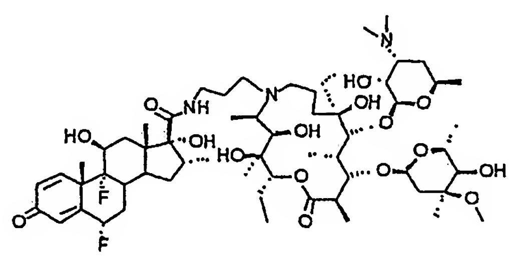
15. Compound 7 according to claims 1, 2 and 6, characterized by the formula



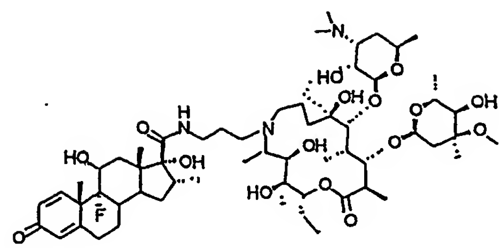
16. Compound 8 according to claims 1, 2 and 6, characterized by the formula



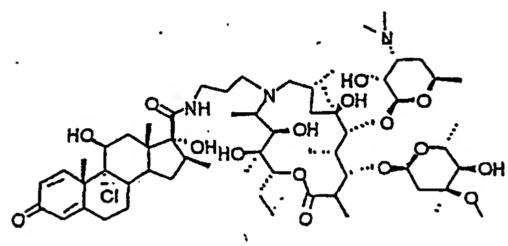
17. Compound 9 according to claims 1, 2 and 6, characterized by the formula



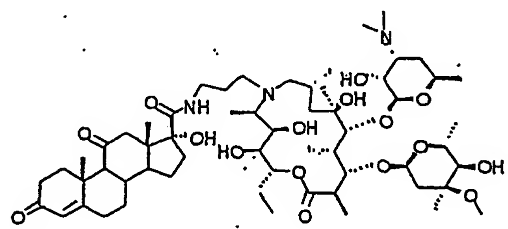
18. Compound 10 according to claims 1, 2 and 6, characterized by the formula



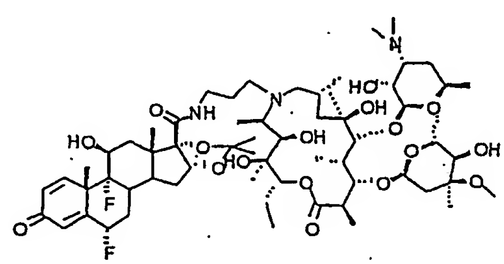
19. Compound 11 according to claims 1, 2 and 6, characterized by the formula



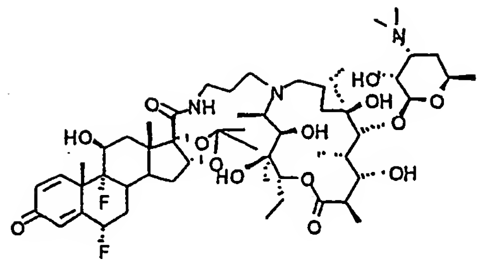
20. Compound 12 according to claims 1, 2 and 6, characterized by the formula



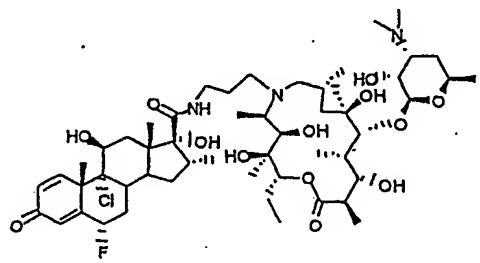
21. Compound 13 according to claims 1, 2 and 6, characterized by the formula



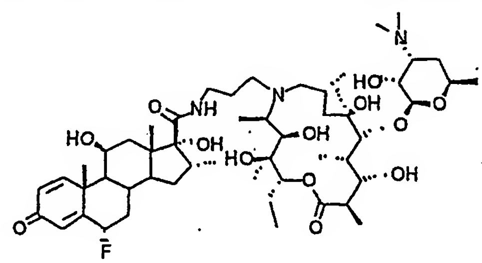
22. Compound 14 according to claims 1, 2 and 6, characterized by the formula



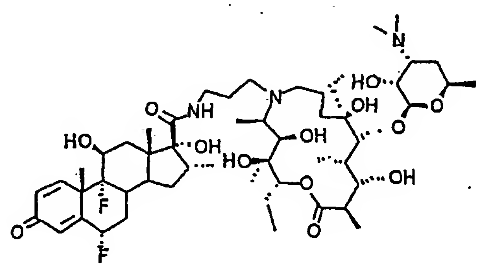
23. Compound 15 according to claims 1, 2 and 6, characterized by the formula



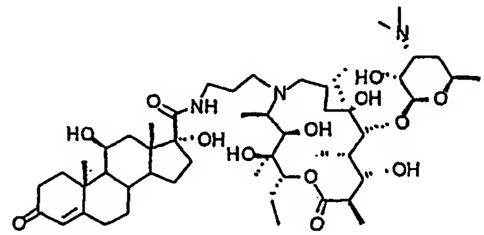
24. Compound 16 according to claims 1, 2 and 6, characterized by the formula



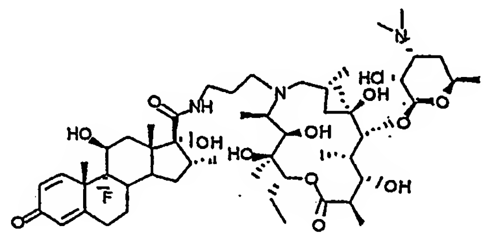
25. Compound 17 according to claims 1, 2 and 6, characterized by the formula



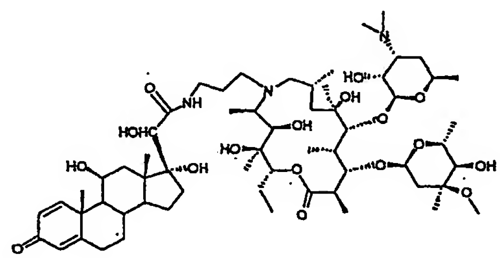
26. Compound 18 according to claims 1, 2 and 6, characterized by the formula



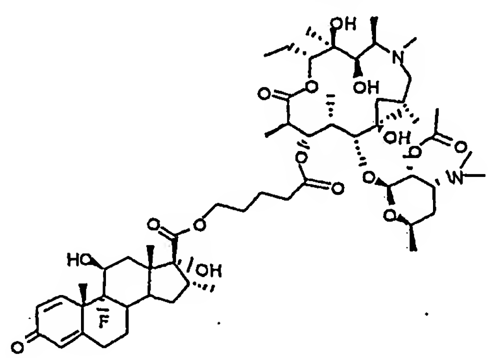
27. Compound 19 according to claims 1, 2 and 6, characterized by the formula



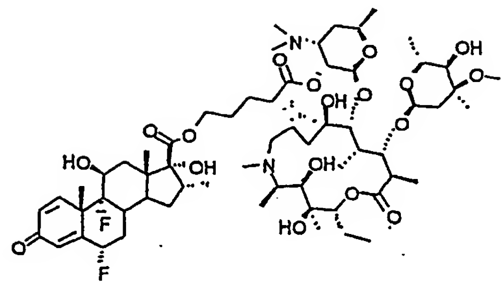
28. Compound 20 according to claims 1, 2 and 6, characterized by the formula



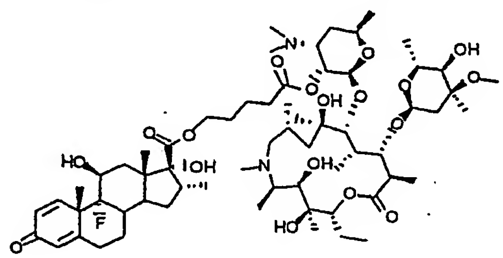
29. Compound 21 according to claims 1, 2 and 4, characterized by the formula



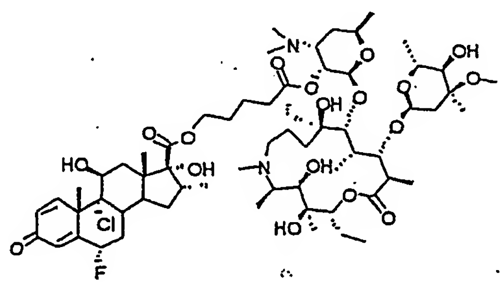
30. Compound 22 according to claims 1, 2 and 7, characterized by the formula



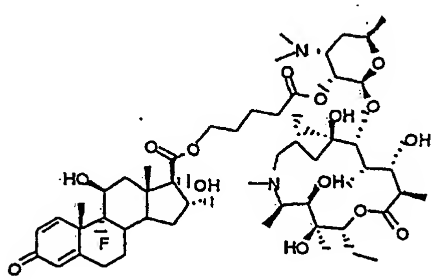
31. Compound 23 according to claims 1, 2 and 7, characterized by the formula



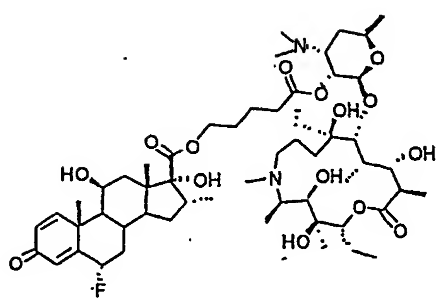
32. Compound 24 according to claims 1, 2 and 7, characterized by the formula



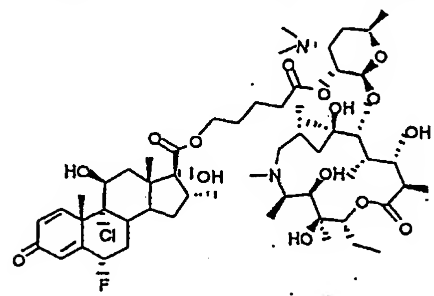
33. Compound 25 according to claims 1, 2 and 7, characterized by the formula



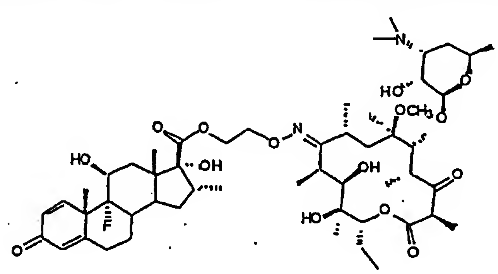
34. Compound 26 according to claims 1, 2 and 7, characterized by the formula



35. Compound 27 according to claims 1, 2 and 7, characterized by the formula



36. Compound 28 according to claims 1, 2 and 3, characterized by the formula



37. Process for the preparation of compounds represented by the general structure I wherein all symbols and radicals have the meanings as defined in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radicals and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, and a macrolide intermediate represented by the structure **M11** by linking them *via* corresponding chains represented by the structure **L**, whereat for the formation of an amide bond from carboxylic acids of the steroid subunits indicated by the formulas **A1** to **A4** and **A6**, activation with carboxydiimide and benzotriazole (HOBT) in anhydrous

dichloromethane in the presence of a base such as triethylamine at room temperature under the flow of a suitable inert gas is used.

38. Process for the preparation of compounds represented by the general structure I, wherein all symbols and radicals have the meanings as defined in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radical and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, and a macrolide intermediate represented by the structure **M7** by linking them *via* corresponding chains represented by the structure **L**, whereat for the formation of an ester bond from carboxylic acids of the steroid subunits indicated by the formulas **A1** to **A4** and **A6**, a reaction with K_2CO_3 in anhydrous dimethylformamide in the flow of a suitable inert gas is used.

39. Process for the preparation of compounds represented by the general structure I, wherein all symbols and radicals have the meanings as defined in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radical and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, and a macrolide intermediate represented by the structure **M9** by linking them *via* corresponding chains represented by the structure **L**, whereat for the formation of an ester bond from carboxylic acids of the steroid subunits indicated by the formulas **A1** to **A4** and **A6**, a reaction with K_2CO_3 in anhydrous dimethylformamide in the flow of a suitable inert gas is used.

40. Process for the preparation of compounds represented by the general structure I, wherein all symbols and radicals have the meanings as stated in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radical and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, and a macrolide intermediate represented by the structure **M10** by linking them *via* corresponding

chains represented by the structure **L**, whereat for the formation of an ester bond from carboxylic acids of the steroid subunits indicated by the formulas **A1** to **A4** and **A6**, a reaction with K_2CO_3 in anhydrous dimethylformamide in the flow of a suitable inert gas is used.

41. Process for the preparation of compounds represented by the general structure I, wherein all symbols and radicals have meanings as defined in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radical and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, with the synthesis being performed by mixing the steroid intermediate **A8** and the macrolide intermediate represented by the structure **M12** in acetonitrile at a temperature from 20 to 60 °C in the flow of a suitable inert gas.

42. Process for the preparation of compounds represented by the general structure I, wherein all symbols and radicals have the meanings as defined in claims 1 and 2, characterized in that the compounds can be prepared from a corresponding steroid part represented by the structures **A1** to **A4** and **A6**, wherein all radical and symbols have the meanings as defined for the substructures **A1** to **A4** and **A6**, with the esterification synthesis being performed using the steroid intermediate **A9** and a macrolide having a free reactive hydroxyl group and mixing them with pivaloyl chloride as an activator at room temperature in the presence of a base such as triethylamine in the flow of a suitable inert gas.

43. Use of compounds according to claims 1 to 36 in human or veterinary medicine.

44. Use of compounds according to claims 1 to 36 in therapy of patients with inflammation conditions and diseases.

45. Use of compounds according to claims 1 to 36 in therapy of patients with asthma, allergic rhinitis, nasal polyps, intestinal diseases such as Crohn's disease, colitis, ulcerative colitis, dermatological inflammations such as eczema, psoriasis, allergic dermatitis, neurodermatitis, pruritis, conjunctivitis and rheumatoid arthritis.

46. Use of compounds according to claims 1 to 36 in treatment and prophylaxis of inflammatory conditions and diseases induced by excessive nonregulated production of cytokines and inflammation mediators, wherein the suitable pharmaceutical preparations can be administered topically, parenterally or orally.

47. Use of compounds according to claims 1 to 36 as active substances in pharmaceutical preparations for oral, rectal, parenteral, percutaneous and inhalation application in humans and animals.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 02/00001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J43/00 A61K31/58 A61P5/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. ROMO ET AL: "Total Synthesis and Immunosuppressive Activity of (-)-Pateamine A and Related Compounds: Implementation of beta-Lactam Based Macrolzyztion" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 120, no. 47, 1998, pages 12237-12254, XP002200620 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 12234, Scheme 12, compound 69 page 12234, column 2, paragraph 2 page 12246, column 1; table 3 ---	2-47
X	WO 97 41255 A (MASSACHUSETTS INST TECHNOLOGY) 6 November 1997 (1997-11-06) figure 7B; example 1 ---	2-47

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2002	18/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GRIFFITH, ERIC C. ET AL: "Yeast three-hybrid system for detecting ligand-receptor interactions" retrieved from STN Database accession no. 135:147811 XP002200621 abstract & METHODS IN ENZYMOLOGY (2000), 328(APPLICATIONS OF CHIMERIC GENES AND HYBRID PROTEINS, PT. C), 89-103 , ---	2-47
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCHENTAG, J. J. ET AL: "Relationships between serum, intracellular, and infection site concentrations of macrolide and azalide antibiotics. A theoretical exploration of the concept of white blood cell drug delivery to infection sites" retrieved from STN Database accession no. 126:135534 XP002200622 abstract & ANTIINFECT. DRUGS CHEMOTHER. (1996), 14(2), 137-146 , ---	2-47
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IWAKI, RIICHIRO: "Analgesic, antiinflammatory, and pus-removing pharmaceuticals" retrieved from STN Database accession no. 112:104876 XP002200623 abstract & JP 01 163124 A (SANYU SEIKATSUSHA K. K., JAPAN) 27 June 1989 (1989-06-27) ---	2-47

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1988 ANDERSON R ET AL: "AN IN-VITRO EVALUATION OF THE CELLULAR UPTAKE AND INTRAPHAGOCYTIC BIOACTIVITY OF CLARITHROMYCIN A-56268 TE-031 A NEW MACROLIDE ANTIMICROBIAL AGENT" Database accession no. PREV198987045431 XP002200624 abstract & JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 22, no. 6, 1988, pages 923-934, ISSN: 0305-7453 ---	2-47
Y	DATABASE MEDLINE 'Online! February 1997 (1997-02) FIETTA A ET AL: "Requirements for intracellular accumulation and release of clarithromycin and azithromycin by human phagocytes." Database accession no. NLM9106014 XP002200625 abstract & JOURNAL OF CHEMOTHERAPY (FLORENCE, ITALY) ITALY FEB 1997, vol. 9, no. 1, February 1997 (1997-02), pages 23-31, ISSN: 1120-009X ---	2-47
Y	DATABASE MEDLINE 'Online! October 1997 (1997-10) VAZIFEH D ET AL: "Cellular accumulation of the new ketolide RU 64004 by human neutrophils: comparison with that of azithromycin and roxithromycin." Database accession no. NLM9333032 XP002200626 abstract & ANTIMICROBIAL AGENTS AND CHEMOTHERAPY. UNITED STATES OCT 1997, vol. 41, no. 10, October 1997 (1997-10), pages 2099-2107, ISSN: 0066-4804 --- -/--	2-47

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 02/00001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE MEDLINE 'Online! 1997 GEERDES-FENGE H F ET AL: "Comparative pharmacokinetics of dirithromycin and erythromycin in normal volunteers with special regard to accumulation in polymorphonuclear leukocytes and in saliva." Database accession no. NLM9403284 XP002200627 abstract & EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY. GERMANY 1997, vol. 53, no. 2, 1997, pages 127-133, ISSN: 0031-6970 ---	2-47
Y	DATABASE MEDLINE 'Online! June 1999 (1999-06) SCORNEAUX B ET AL: "Intracellular accumulation, subcellular distribution, and efflux of tilmicosin in bovine mammary, blood, and lung cells." Database accession no. NLM10386306 XP002200628 abstract & JOURNAL OF DAIRY SCIENCE. UNITED STATES JUN 1999, vol. 82, no. 6, June 1999 (1999-06), pages 1202-1212, ISSN: 0022-0302 ---	2-47
Y	DATABASE MEDLINE 'Online! March 1999 (1999-03) KHOSLA R ET AL: "Streptogramins: a new class of antibiotics." Database accession no. NLM10798011 XP002200629 abstract & INDIAN JOURNAL OF MEDICAL SCIENCES. INDIA MAR 1999, vol. 53, no. 3, March 1999 (1999-03), pages 111-119, ISSN: 0019-5359 ---	2-47
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IANARO, ANGELA ET AL: "Anti- inflammatory activity of macrolide antibiotics" retrieved from STN Database accession no. 132:160867 XP002200630 abstract & JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (2000), 292(1), 156-163 , ---	2-47
	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ABDELGHAFFAR, HOURIA ET AL: "Erythromycin A-derived macrolides modify the functional activities of human neutrophils by altering the phospholipase D-phosphatidate phosphohydrolase transduction pathway. L-Cladinose is involved both in alterations of neutrophil functions and modulation of this transductional pathway" retrieved from STN Database accession no. 127:341381 XP002200631 abstract & J. IMMUNOL. (1997), 159(8), 3995-4005 , ---	2-47
Y	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TRAVERS, JEFFREY B.: "Novel immunomodulators for topical skin disease therapy" retrieved from STN Database accession no. 132:189221 XP002200632 abstract & EXPERT OPINION ON INVESTIGATIONAL DRUGS (2000), 9(3), 529-542 , ---	2-47
Y	WO 99 64040 A (ADVANCED MEDICINE INC ;GRIFFIN JOHN H (US); JUDICE J KEVIN (US)) 16 December 1999 (1999-12-16) page 34, paragraph 1 page 68, line 24 -page 69, line 15 ---	2-47
Y	FR 2 776 927 A (UNIV PARIS CURIE) 8 October 1999 (1999-10-08) page 5, paragraph 3; claim 1 page 7, paragraph 1 page 16, paragraphs 3,4 -----	2-47

INTERNATIONAL SEARCH REPORT

Ional Application No
PCT/HR 02/00001

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9741255	A	06-11-1997	CA	2252886 A1	06-11-1997
			EP	0907750 A1	14-04-1999
			JP	2000508923 T	18-07-2000
			WO	9741255 A1	06-11-1997
			US	5928868 A	27-07-1999
JP 1163124	A	27-06-1989	NONE		
WO 9964040	A	16-12-1999	AU	4543799 A	30-12-1999
			AU	4544099 A	30-12-1999
			AU	4549999 A	30-12-1999
			CA	2318547 A1	16-12-1999
			CA	2319085 A1	16-12-1999
			EP	1086065 A1	28-03-2001
			EP	1079845 A1	07-03-2001
			WO	9964032 A1	16-12-1999
			WO	9964036 A1	16-12-1999
			WO	9964040 A1	16-12-1999
FR 2776927	A	08-10-1999	FR	2776927 A1	08-10-1999
			CA	2327737 A1	14-10-1999
			EP	1067969 A1	17-01-2001
			WO	9951274 A1	14-10-1999
			PL	343365 A1	13-08-2001